

EXHIBIT 10

Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

Wylie C. Hembree,¹ Peggy T. Cohen-Kettenis,² Louis Gooren,³ Sabine E. Hannema,⁴ Walter J. Meyer,⁵ M. Hassan Murad,⁶ Stephen M. Rosenthal,⁷ Joshua D. Safer,⁸ Vin Tangpricha,⁹ and Guy G. T'Sjoen¹⁰

¹New York Presbyterian Hospital, Columbia University Medical Center, New York, New York 10032 (Retired); ²VU University Medical Center, 1007 MB Amsterdam, Netherlands (Retired); ³VU University Medical Center, 1007 MB Amsterdam, Netherlands (Retired); ⁴Leiden University Medical Center, 2300 RC Leiden, Netherlands; ⁵University of Texas Medical Branch, Galveston, Texas 77555; ⁶Mayo Clinic Evidence-Based Practice Center, Rochester, Minnesota 55905; ⁷University of California San Francisco, Benioff Children's Hospital, San Francisco, California 94143; ⁸Boston University School of Medicine, Boston, Massachusetts 02118; ⁹Emory University School of Medicine and the Atlanta VA Medical Center, Atlanta, Georgia 30322; and ¹⁰Ghent University Hospital, 9000 Ghent, Belgium

***Cosponsoring Associations:** American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society-appointed task force of nine experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusion: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments—appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health

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Abbreviations: BMD, bone mineral density; DSD, disorder/difference of sex development; DSM, Diagnostic and Statistical Manual of Mental Disorders; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; MHP, mental health professional; VTE, venous thromboembolism.

professional for adults (recommended)—should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment. (*J Clin Endocrinol Metab* 102: 3869–3903, 2017)

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Summary of Recommendations

1.0 Evaluation of youth and adults

- 1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)
- 1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)
- 1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

- 1.4. We recommend against puberty blocking and gender-affirming hormone treatment in pre-pubertal children with GD/gender incongruence. (1 I⊕⊕○○)
- 1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 I⊕⊕○○)

2.0 Treatment of adolescents

- 2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 I⊕⊕○○)
- 2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 I⊕⊕○○)
- 2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 I⊕⊕○○)
- 2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 I⊕⊕○○).
- 2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥ 16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 I⊕○○○)
- 2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 I⊕⊕○○)

3.0 Hormonal therapy for transgender adults

- 3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and

- the criteria for the endocrine phase of gender transition before beginning treatment. (1 I⊕⊕⊕○)
- 3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 I⊕⊕○○)
- 3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 I⊕⊕○○)
- 3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 I⊕○○○)

4.0 Adverse outcome prevention and long-term care

- 4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 I⊕⊕○○)
- 4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 I⊕⊕○○)
- 4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 I⊕⊕○○)
- 4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 I⊕⊕○○)
- 4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 I⊕⊕○○)
- 4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 I⊕○○○)
- 4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

5.0 Surgery for sex reassignment and gender confirmation

- 5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 $\text{I} \oplus \text{O} \text{O}$)
- 5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)
- 5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)
- 5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 $\text{I} \oplus \text{O} \text{O}$)
- 5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 $\text{I} \oplus \text{O} \text{O}$).
- 5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 $\text{I} \oplus \text{O} \text{O}$)

Changes Since the Previous Guideline

Both the current guideline and the one published in 2009 contain similar sections. Listed here are the sections contained in the current guideline and the corresponding number of recommendations: Introduction, Evaluation of Youth and Adults (5), Treatment of Adolescents (6), Hormonal Therapy for Transgender Adults (4), Adverse Outcomes Prevention and Long-term Care (7), and Surgery for Sex Reassignment and Gender Confirmation (6). The current introduction updates the diagnostic classification of “gender dysphoria/gender incongruence.” It also reviews the development of “gender identity” and summarizes its natural development. The section on

clinical evaluation of both youth and adults, defines in detail the professional qualifications required of those who diagnose and treat both adolescents and adults. We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional. We recommend against puberty blocking followed by gender-affirming hormone treatment of prepubertal children. Clinicians should inform pubertal children, adolescents, and adults seeking gender-Confirming treatment of their options for fertility preservation. Prior to treatment, clinicians should evaluate the presence of medical conditions that may be worsened by hormone depletion and/or treatment. A multidisciplinary team, preferably composed of medical and mental health professionals, should monitor treatments. Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence. Physicians should educate transgender persons regarding the time course of steroid-induced physical changes. Treatment should include periodic monitoring of hormone levels and metabolic parameters, as well as assessments of bone density and the impact upon prostate, gonads, and uterus. We also make recommendations for transgender persons who plan genital gender-affirming surgery.

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of individuals with GD/gender incongruence a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence, such that $\text{O} \text{O} \text{O}$ denotes very low-quality evidence; $\text{I} \oplus \text{O} \text{O}$, low quality; $\text{I} \oplus \text{O} \text{O}$, moderate quality; and $\text{I} \oplus \text{O} \text{O} \text{O}$, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Weak recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the

values that the task force considered in making the recommendation. In some instances, there are remarks in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision-making, general preventive care measures, and basic principles of the treatment of transgender persons. They labeled these “Ungraded Good Practice Statement.” Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to these principles.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society’s Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline’s development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The CGS and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.*, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers’ bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Review

The task force commissioned two systematic reviews to support this guideline. The first one aimed to summarize the available evidence on the effect of sex steroid use in transgender individuals on lipids and cardiovascular outcomes. The review identified 29 eligible studies at moderate risk of bias. In transgender males (female to male), sex steroid therapy was associated with a statistically significant increase in serum triglycerides and low-density lipoprotein cholesterol levels. High-density lipoprotein cholesterol levels decreased significantly across all follow-up time periods. In transgender females (male to female), serum triglycerides were significantly higher without any changes in other parameters. Few myocardial infarction, stroke, venous thromboembolism (VTE), and death events were reported. These events were more frequent in transgender females. However, the

quality of the evidence was low. The second review summarized the available evidence regarding the effect of sex steroids on bone health in transgender individuals and identified 13 studies. In transgender males, there was no statistically significant difference in the lumbar spine, femoral neck, or total hip BMD at 12 and 24 months compared with baseline values before initiating masculinizing hormone therapy. In transgender females, there was a statistically significant increase in lumbar spine BMD at 12 months and 24 months compared with baseline values before initiation of feminizing hormone therapy. There was minimal information on fracture rates. The quality of evidence was also low.

Introduction

Throughout recorded history (in the absence of an endocrine disorder) some men and women have experienced confusion and anguish resulting from rigid, forced conformity to sexual dimorphism. In modern history, there have been numerous ongoing biological, psychological, cultural, political, and sociological debates over various aspects of gender variance. The 20th century marked the emergence of a social awakening for men and women with the belief that they are “trapped” in the wrong body (3). Magnus Hirschfeld and Harry Benjamin, among others, pioneered the medical responses to those who sought relief from and a resolution to their profound discomfort. Although the term transsexual became widely known after Benjamin wrote “The Transsexual Phenomenon” (4), it was Hirschfeld who coined the term “transsexual” in 1923 to describe people who want to live a life that corresponds with their experienced gender vs their designated gender (5). Magnus Hirschfeld (6) and others (4, 7) have described other types of trans phenomena besides transsexualism. These early researchers proposed that the gender identity of these people was located somewhere along a unidimensional continuum. This continuum ranged from all male through “something in between” to all female. Yet such a classification does not take into account that people may have gender identities outside this continuum. For instance, some experience themselves as having both a male and female gender identity, whereas others completely renounce any gender classification (8, 9). There are also reports of individuals experiencing a continuous and rapid involuntary alternation between a male and female identity (10) or men who do not experience themselves as men but do not want to live as women (11, 12). In some countries, (*e.g.*, Nepal, Bangladesh, and Australia), these nonmale or nonfemale genders are officially recognized (13). Specific treatment protocols, however, have not yet been developed for these groups.

Instead of the term transsexualism, the current classification system of the American Psychiatric Association uses the term gender dysphoria in its diagnosis of persons who are not satisfied with their designated gender (14). The current version of the World Health Organization's ICD-10 still uses the term transsexualism when diagnosing adolescents and adults. However, for the ICD-11, the World Health Organization has proposed using the term "gender incongruence" (15).

Treating persons with GD/gender incongruence (15) was previously limited to relatively ineffective elixirs or creams. However, more effective endocrinology-based treatments became possible with the availability of testosterone in 1935 and diethylstilbestrol in 1938. Reports of individuals with GD/gender incongruence who were treated with hormones and gender-affirming surgery appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association was founded in September 1979 and is now called the World Professional Association for Transgender Health (WPATH). WPATH published its first Standards of Care in 1979. These standards have since been regularly updated, providing guidance for treating persons with GD/gender incongruence (16).

Prior to 1975, few peer-reviewed articles were published concerning endocrine treatment of transgender persons. Since then, more than two thousand articles about various aspects of transgender care have appeared.

It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with GD/gender incongruence.

In the future, we need more rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols. Specifically, endocrine treatment protocols for GD/gender incongruence should include the careful assessment of the following: (1) the effects of prolonged delay of puberty in adolescents on bone health, gonadal function, and the brain (including effects on cognitive, emotional, social, and sexual development); (2) the effects of treatment in adults on sex hormone levels; (3) the requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids during treatment; and (4) the risks and benefits of gender-affirming hormone treatment in older transgender people.

To successfully establish and enact these protocols, a commitment of mental health and endocrine investigators is required to collaborate in long-term, large-scale

studies across countries that use the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools (e.g., the European Network for the Investigation of Gender Incongruence) (17, 18).

Terminology and its use vary and continue to evolve. Table 1 contains the definitions of terms as they are used throughout this guideline.

Biological Determinants of Gender Identity Development

One's self-awareness as male or female changes gradually during infant life and childhood. This process of cognitive and affective learning evolves with interactions with parents, peers, and environment. A fairly accurate timetable exists outlining the steps in this process (19). Normative psychological literature, however, does not address if and when gender identity becomes crystallized and what factors contribute to the development of a gender identity that is not congruent with the gender of rearing. Results of studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomic—support the concept that gender identity and/or gender expression (20) likely reflect a complex interplay of biological, environmental, and cultural factors (21, 22).

With respect to endocrine considerations, studies have failed to find differences in circulating levels of sex steroids between transgender and nontransgender individuals (23). However, studies in individuals with a disorder/difference of sex development (DSD) have informed our understanding of the role that hormones may play in gender identity outcome, even though most persons with GD/gender incongruence do not have a DSD. For example, although most 46,XX adult individuals with virilizing congenital adrenal hyperplasia caused by mutations in *CYP21A2* reported a female gender identity, the prevalence of GD/gender incongruence was much greater in this group than in the general population without a DSD. This supports the concept that there is a role for prenatal/postnatal androgens in gender development (24–26), although some studies indicate that prenatal androgens are more likely to affect gender behavior and sexual orientation rather than gender identity *per se* (27, 28).

Researchers have made similar observations regarding the potential role of androgens in the development of gender identity in other individuals with DSD. For example, a review of two groups of 46,XY persons, each with androgen synthesis deficiencies and female raised, reported transgender male (female-to-male) gender role changes in 56% to 63% and 39% to 64% of patients, respectively (29). Also, in 46,XY female-raised individuals with cloacal

Table 1. Definitions of Terms Used in This Guideline

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| Biological sex, biological male or female: These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (e.g., a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided. |
| Cisgender: This means not transgender. An alternative way to describe individuals who are not transgender is "non-transgender people." |
| Gender-affirming (hormone) treatment: See "gender reassignment" |
| Gender dysphoria: This is the distress and unease experienced if gender identity and designated gender are not completely congruent (see Table 2). In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced "gender identity disorder" with "gender dysphoria" and changed the criteria for diagnosis. |
| Gender expression: This refers to external manifestations of gender, expressed through one's name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender. |
| Gender identity/experienced gender: This refers to one's internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below), gender identity is not visible to others. |
| Gender identity disorder: This is the term used for GD/gender incongruence in previous versions of DSM (see "gender dysphoria"). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using "gender incongruence of childhood." |
| Gender incongruence: This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity-related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment. |
| Gender variance: See "gender incongruence" |
| Gender reassignment: This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called gender-confirming or gender-affirming treatment. |
| Gender-reassignment surgery (gender-confirming/gender-affirming surgery): These terms refer only to the surgical part of gender-confirming/gender-affirming treatment. |
| Gender role: This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women. |
| Sex designated at birth: This refers to sex assigned at birth, usually based on genital anatomy. |
| Sex: This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics. |
| Sexual orientation: This term describes an individual's enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer. |
| Transgender: This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment. |
| Transgender male (also: trans man, female-to-male, transgender male): This refers to individuals assigned female at birth but who identify and live as men. |
| Transgender woman (also: trans woman, male-to female, transgender female): This refers to individuals assigned male at birth but who identify and live as women. |
| Transition: This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially. |
| Transsexual: This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so. |

exstrophy and penile agenesis, the occurrence of transgender male changes was significantly more prevalent than in the general population (30, 31). However, the fact that a high percentage of individuals with the same conditions did not change gender suggests that cultural factors may play a role as well.

With respect to genetics and gender identity, several studies have suggested heritability of GD/gender incongruence (32, 33). In particular, a study by Heylens *et al.* (33) demonstrated a 39.1% concordance rate for gender identity disorder (based on the DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs. Although numerous investigators have sought to identify

specific genes associated with GD/gender incongruence, such studies have been inconsistent and without strong statistical significance (34–38).

Studies focusing on brain structure suggest that the brain phenotypes of people with GD/gender incongruence differ in various ways from control males and females, but that there is not a complete sex reversal in brain structures (39).

In summary, although there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental factors, contribute to this fundamental aspect of human development.

Natural History of Children With GD/Gender Incongruence

With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called “desisters”). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence (20, 40). In adolescence, a significant number of these desisters identify as homosexual or bisexual. It may be that children who only showed some gender nonconforming characteristics have been included in the follow-up studies, because the DSM-IV text revision criteria for a diagnosis were rather broad. However, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (41, 42). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy. Together with an MHP, hormone-prescribing clinicians should examine the psychosocial impact of the potential changes on people’s lives, including mental health, friends, family, jobs, and their role in society. Transgender individuals should be encouraged to experience living in the new gender role and assess whether

this improves their quality of life. Although the focus of this guideline is gender-affirming hormone therapy, collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome.

Diagnostic assessment and mental health care

GD/gender incongruence may be accompanied with psychological or psychiatric problems (43–51). It is therefore necessary that clinicians who prescribe hormones and are involved in diagnosis and psychosocial assessment meet the following criteria: (1) are competent in using the DSM and/or the ICD for diagnostic purposes, (2) are able to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder), (3) are trained in diagnosing psychiatric conditions, (4) undertake or refer for appropriate treatment, (5) are able to do a psychosocial assessment of the patient’s understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) regularly attend relevant professional meetings.

Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex.

During assessment, the clinician obtains information from the individual seeking gender-affirming treatment. In the case

Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A. A marked incongruence between one’s experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following: |
| 1. A marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics) |
| 2. A strong desire to be rid of one’s primary and/or secondary sex characteristics because of a marked incongruence with one’s experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics) |
| 3. A strong desire for the primary and/or secondary sex characteristics of the other gender |
| 4. A strong desire to be of the other gender (or some alternative gender different from one’s designated gender) |
| 5. A strong desire to be treated as the other gender (or some alternative gender different from one’s designated gender) |
| 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one’s designated gender) |
| B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning. |
| Specify if: |
| 1. The condition exists with a disorder of sex development. |
| 2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females). |

Reference: American Psychiatric Association (14).

of adolescents, the clinician also obtains information from the parents or guardians regarding various aspects of the child's general and psychosexual development and current functioning. On the basis of this information, the clinician:

- decides whether the individual fulfills criteria for treatment (see Tables 2 and 3) for GD/gender incongruence (DSM-5) or transsexualism (DSM-5 and/or ICD-10);
- informs the individual about the possibilities and limitations of various kinds of treatment (hormonal/surgical and nonhormonal), and if medical treatment is desired, provides correct information to prevent unrealistically high expectations;
- assesses whether medical interventions may result in unfavorable psychological and social outcomes.

In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with positive outcomes (52–56).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (57) and an assessment of the decision-making capability of the youth. An evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic phase (58).

Social transitioning

A change in gender expression and role (which may involve living part time or full time in another gender role that is consistent with one's gender identity) may test the person's resolve, the capacity to function in the affirmed gender, and the adequacy of social, economic, and psychological supports. It assists both the individual and the clinician in their judgments about how to proceed (16). During social transitioning, the person's feelings about the social transformation (including coping with the responses of others) is a major focus of the counseling. The optimal timing for social transitioning may differ between individuals. Sometimes people wait until they

start gender-affirming hormone treatment to make social transitioning easier, but individuals increasingly start social transitioning long before they receive medically supervised, gender-affirming hormone treatment.

Criteria

Adolescents and adults seeking gender-affirming hormone treatment and surgery should satisfy certain criteria before proceeding (16). Criteria for gender-affirming hormone therapy for adults are in Table 4, and criteria for gender-affirming hormone therapy for adolescents are in Table 5. Follow-up studies in adults meeting these criteria indicate a high satisfaction rate with treatment (59). However, the quality of evidence is usually low. A few follow-up studies on adolescents who fulfilled these criteria also indicated good treatment results (60–63).

Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence

1. We advise that only trained MHPs who meet the following criteria should diagnose GD/gender incongruence in adults: (1) competence in using the DSM and/or the ICD for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)
2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or ICD for diagnostic

Table 3. ICD-10 Criteria for Transsexualism

Transsexualism (F64.0) has three criteria:

1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 y.
3. The disorder is not a symptom of another mental disorder or a genetic, DSD, or chromosomal abnormality.

Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (43–48, 50, 51, 64, 65). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (66), or certain forms of eunuchism (in which a person is preoccupied with or engages in castration and/or penectomy for

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
 - the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
 - gender dysphoria worsened with the onset of puberty,
 - any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
 - the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,
2. And the adolescent:
 - has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
 - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
 - agrees with the indication for GnRH agonist treatment,
 - has confirmed that puberty has started in the adolescent (Tanner stage \geq G2/B2),
 - has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
 - the persistence of gender dysphoria,
 - any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
 - the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
2. And the adolescent:
 - has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
 - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
 - agrees with the indication for sex hormone treatment,
 - has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

reasons that are not gender identity related) (11). Clinicians should also be able to diagnose psychiatric conditions accurately and ensure that these conditions are treated appropriately, particularly when the conditions may complicate treatment, affect the outcome of gender-affirming treatment, or be affected by hormone use.

Values and preferences

The task force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the good practice statement.

- 1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).
- 1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 I⊕⊕OO)

Evidence

In most children diagnosed with GD/gender incongruence, it did not persist into adolescence. The percentages differed among studies, probably dependent on which version of the DSM clinicians used, the patient's age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/gender incongruent in adolescence (20). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (40). Social transition is associated with the persistence of GD/gender incongruence as a child progresses into adolescence. It may be that the presence of GD/gender incongruence in prepubertal children is the earliest sign that a child is destined to be transgender as an adolescent/adult (20). However, social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence.

This recommendation, however, does not imply that children should be discouraged from showing gender-variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the

GD/gender-incongruent children to whom this applies. At the present time, clinical experience suggests that persistence of GD/gender incongruence can only be reliably assessed after the first signs of puberty.

Values and preferences

The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence. This justifies the strong recommendation in the face of low-quality evidence.

- 1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 I⊕⊕⊕O)

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (67, 68). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding the future fertility of adolescents or adults beginning gender-affirming treatment.

Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option. This option is often not preferred, because mature sperm production is associated with later stages of puberty and with the significant development of secondary sex characteristics.

For those designated male at birth with GD/gender incongruence and who are in early puberty, sperm production and the development of the reproductive tract are insufficient for the cryopreservation of sperm. However, prolonged pubertal suppression using GnRH analogs is reversible and clinicians should inform these individuals that sperm production can be initiated following prolonged gonadotropin suppression. This can be accomplished by spontaneous gonadotropin recovery after

cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production, as stated above. Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In males treated for precocious puberty, spermatarche was reported 0.7 to 3 years after cessation of GnRH analogs (69). In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6 to 12 months of gonadotropin treatment. However, sperm numbers when partners of these patients conceive are far below the “normal range” (70, 71).

In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (72, 73). Clinicians should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression.

In males with GD/gender incongruence, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis is currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In females with GD/gender incongruence, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender males, both prior to and as a result of androgen treatment (74–77), although these reports were not confirmed by others (78). Pregnancy has been reported in transgender males who have had prolonged androgen treatment and have discontinued testosterone but have not had genital surgery (79, 80). A reproductive endocrine gynecologist can counsel patients before gender-affirming hormone treatment or surgery regarding potential fertility options (81). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve, and oocyte maturation of immature tissue is being studied (82).

2.0 Treatment of Adolescents

During the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. However, for many adolescents with GD/gender incongruence, the pubertal physical changes are unbearable. As early medical intervention may prevent

psychological harm, various clinics have decided to start treating young adolescents with GD/gender incongruence with puberty-suppressing medication (a GnRH analog). As compared with starting gender-affirming treatment long after the first phases of puberty, a benefit of pubertal suppression at early puberty may be a better psychological and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche occurs ~2 years later. In boys, the first physical change is testicular growth. A testicular volume ≥ 4 mL is seen as consistent with the initiation of physical puberty. At the beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early morning with an ultrasensitive assay. From a testicular volume of 10 mL, daytime testosterone levels increase, leading to virilization (83). Note that pubic hair and/or axillary hair/odor may not reflect the onset of gonadarche; instead, it may reflect adrenarche alone.

- 2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment (Table 5), and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 I⊕⊕○○)
- 2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty (Tanner stages G2/B2). (2 I⊕⊕○○)

Evidence

Pubertal suppression can expand the diagnostic phase by a long period, giving the subject more time to explore options and to live in the experienced gender before making a decision to proceed with gender-affirming sex hormone treatments and/or surgery, some of which is irreversible (84, 85). Pubertal suppression is fully reversible, enabling full pubertal development in the natal gender, after cessation of treatment, if appropriate. The experience of full endogenous puberty is an undesirable condition for the GD/gender-incongruent individual and may seriously interfere with healthy psychological functioning and well-being. Treating GD/gender-incongruent adolescents entering puberty with GnRH analogs has been shown to improve psychological functioning in several domains (86).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared with initiating physical transition after puberty has been completed (60, 62). Looking like a man or woman when living as the opposite sex creates difficult

barriers with enormous life-long disadvantages. We therefore advise starting suppression in early puberty to prevent the irreversible development of undesirable secondary sex characteristics. However, adolescents with GD/gender incongruence should experience the first changes of their endogenous spontaneous puberty, because their emotional reaction to these first physical changes has diagnostic value in establishing the persistence of GD/gender incongruence (85). Thus, Tanner stage 2 is the optimal time to start pubertal suppression. However, pubertal suppression treatment in early puberty will limit the growth of the penis and scrotum, which will have a potential effect on future surgical treatments (87).

Clinicians can also use pubertal suppression in adolescents in later pubertal stages to stop menses in transgender males and prevent facial hair growth in transgender females. However, in contrast to the effects in early pubertal adolescents, physical sex characteristics (such as more advanced breast development in transgender boys and lowering of the voice and outgrowth of the jaw and brow in transgender girls) are not reversible.

Values and preferences

These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression.

Remarks

Table 6 lists the Tanner stages of breast and male genital development. Careful documentation of hallmarks of pubertal development will ensure precise timing when initiating pubertal suppression once puberty has started. Clinicians can use pubertal LH and sex steroid levels to confirm that puberty has progressed sufficiently before starting pubertal suppression (88). Reference

ranges for sex steroids by Tanner stage may vary depending on the assay used. Ultrasensitive sex steroid and gonadotropin assays will help clinicians document early pubertal changes.

Irreversible and, for GD/gender-incongruent adolescents, undesirable sex characteristics in female puberty are breasts, female body habitus, and, in some cases, relative short stature. In male puberty, they are a prominent Adam's apple; low voice; male bone configuration, such as a large jaw, big feet and hands, and tall stature; and male hair pattern on the face and extremities.

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 I⊕⊕○○)

Evidence

Clinicians can suppress pubertal development and gonadal function most effectively via gonadotropin suppression using GnRH analogs. GnRH analogs are long-acting agonists that suppress gonadotropins by GnRH receptor desensitization after an initial increase of gonadotropins during ~10 days after the first and (to a lesser degree) the second injection (89). Antagonists immediately suppress pituitary gonadotropin secretion (90, 91). Long-acting GnRH analogs are the currently preferred treatment option. Clinicians may consider long-acting GnRH antagonists when evidence on their safety and efficacy in adolescents becomes available.

During GnRH analog treatment, slight development of secondary sex characteristics may regress, and in a later phase of pubertal development, it will stop. In girls, breast tissue will become atrophic, and menses will stop. In boys, virilization will stop, and testicular volume may decrease (92).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploration of his/her transition wish, the individual no longer desires transition, they can discontinue pubertal suppression. In subjects with

Table 6. Tanner Stages of Breast Development and Male External Genitalia

The description of Tanner stages for breast development:

1. Prepubertal
2. Breast and papilla elevated as small mound; areolar diameter increased
3. Breast and areola enlarged, no contour separation
4. Areola and papilla form secondary mound
5. Mature; nipple projects, areola part of general breast contour

For penis and testes:

1. Prepubertal, testicular volume <4 mL
2. Slight enlargement of penis; enlarged scrotum, pink, texture altered, testes 4–6 mL
3. Penis longer, testes larger (8–12 mL)
4. Penis and glans larger, including increase in breadth; testes larger (12–15 mL), scrotum dark
5. Penis adult size; testicular volume > 15 mL

Adapted from Lawrence (56).

precocious puberty, spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH analogs (93).

Recommendations 2.1 to 2.3 are supported by a prospective follow-up study from The Netherlands. This report assessed mental health outcomes in 55 transgender adolescents/young adults (22 transgender females and 33 transgender males) at three time points: (1) before the start of GnRH agonist (average age of 14.8 years at start of treatment), (2) at initiation of gender-affirming hormones (average age of 16.7 years at start of treatment), and (3) 1 year after “gender-reassignment surgery” (average age of 20.7 years) (63). Despite a decrease in depression and an improvement in general mental health functioning, GD/gender incongruence persisted through pubertal suppression, as previously reported (86). However, following sex hormone treatment and gender-reassignment surgery, GD/gender incongruence was resolved and psychological functioning steadily improved (63). Furthermore, well-being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long-term follow-up of individuals managed according to currently existing clinical practice guidelines for transgender youth, and it underscores the benefit of the multidisciplinary approach pioneered in The Netherlands; however, further studies are needed.

Side effects

The primary risks of pubertal suppression in GD/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development. Few data are available on the effect of GnRH analogs on BMD in adolescents with GD/gender incongruence. Initial data in GD/gender-incongruent subjects demonstrated no change of absolute areal BMD during 2 years of GnRH analog therapy but a decrease in BMD *z* scores (85). A recent study also suggested suboptimal bone mineral accrual during GnRH analog treatment. The study reported a decrease in areal BMD *z* scores and of bone mineral apparent density *z* scores (which takes the size of the bone into account) in 19 transgender males treated with GnRH analogs from a mean age of 15.0 years (standard deviation = 2.0 years) for a median duration of 1.5 years (0.3 to 5.2 years) and in 15 transgender females treated from 14.9 (± 1.9) years for 1.3 years (0.5 to 3.8 years), although not all changes were statistically significant (94). There was incomplete catch-up at age 22 years after sex hormone treatment from age 16.6 (± 1.4

years for a median duration of 5.8 years (3.0 to 8.0 years) in transgender females and from age 16.4 (± 2.3) years for 5.4 years (2.8 to 7.8 years) in transgender males. Little is known about more prolonged use of GnRH analogs. Researchers reported normal BMD *z* scores at age 35 years in one individual who used GnRH analogs from age 13.7 years until age 18.6 years before initiating sex hormone treatment (65).

Additional data are available from individuals with late puberty or GnRH analog treatment of other indications. Some studies reported that men with constitutionally delayed puberty have decreased BMD in adulthood (95). However, other studies reported that these men have normal BMD (96, 97). Treating adults with GnRH analogs results in a decrease of BMD (98). In children with central precocious puberty, treatment with GnRH analogs has been found to result in a decrease of BMD during treatment by some (99) but not others (100). Studies have reported normal BMD after discontinuing therapy (69, 72, 73, 101, 102). In adolescents treated with growth hormone who are small for gestational age and have normal pubertal timing, 2-year GnRH analog treatments did not adversely affect BMD (103). Calcium supplementation may be beneficial in optimizing bone health in GnRH analog-treated individuals (104). There are no studies of vitamin D supplementation in this context, but clinicians should offer supplements to vitamin D-deficient adolescents. Physical activity, especially during growth, is important for bone mass in healthy individuals (103) and is therefore likely to be beneficial for bone health in GnRH analog-treated subjects.

GnRH analogs did not induce a change in body mass index standard deviation score in GD/gender-incongruent adolescents (94) but caused an increase in fat mass and decrease in lean body mass percentage (92). Studies in girls treated for precocious puberty also reported a stable body mass index standard deviation score during treatment (72) and body mass index and body composition comparable to controls after treatment (73).

Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRH analogs for precocious/early puberty (105, 106). Blood pressure monitoring before and during treatment is recommended.

Individuals may also experience hot flashes, fatigue, and mood alterations as a consequence of pubertal suppression. There is no consensus on treatment of these side effects in this context.

It is recommended that any use of pubertal blockers (and subsequent use of sex hormones, as detailed below) include a discussion about implications for fertility (see recommendation 1.3). Transgender adolescents may

want to preserve fertility, which may be otherwise compromised if puberty is suppressed at an early stage and the individual completes phenotypic transition with the use of sex hormones.

Limited data are available regarding the effects of GnRH analogs on brain development. A single cross-sectional study demonstrated no compromise of executive function (107), but animal data suggest there may be an effect of GnRH analogs on cognitive function (108).

Values and preferences

Our recommendation of GnRH analogs places a higher value on the superior efficacy, safety, and reversibility of the pubertal hormone suppression achieved (as compared with the alternatives) and a relatively lower value on limiting the cost of therapy. Of the available alternatives, depot and oral progestin preparations are effective. Experience with this treatment dates back prior to the emergence of GnRH analogs for treating precocious puberty in papers from the 1960s and early 1970s (109–112). These compounds are usually safe, but some side effects have been reported (113–115). Only two recent studies involved transgender youth (116, 117). One of these studies described the use of oral lynestrenol monotherapy followed by the addition of testosterone treatment in transgender boys who were at Tanner stage B4 or further at the start of treatment (117). They found lynestrenol safe, but gonadotropins were not fully suppressed. The study reported metrorrhagia in approximately half of the individuals, mainly in the first 6 months. Acne, headache, hot flashes, and fatigue were other frequent side effects. Another progestin that has been studied in the United States is medroxyprogesterone. This agent is not as effective as GnRH analogs in lowering endogenous sex hormones either and may be associated with other side effects (116). Progestin preparations may be an acceptable treatment for persons without access to GnRH analogs or with a needle phobia. If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see adult section).

Remarks

Measurements of gonadotropin and sex steroid levels give precise information about gonadal axis suppression, although there is insufficient evidence for any specific short-term monitoring scheme in children treated with GnRH analogs (88). If the gonadal axis is not completely suppressed—as evidenced by (for example) menses, erections, or progressive hair growth—the interval of GnRH analog treatment can be shortened or the dose increased. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Table 7 illustrates a suggested clinical protocol.

Anthropometric measurements and X-rays of the left hand to monitor bone age are informative for evaluating growth. To assess BMD, clinicians can perform dual-energy X-ray absorptiometry scans.

- 2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule (see Table 8) after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years (Table 5). (1 I⊕⊕OO)
- 2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥ 16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 I⊕OOO)
- 2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment (Table 9). (2 I⊕⊕OO)

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Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

| | |
|---------------|----------------------------------------------------------------------------------------|
| Every 3–6 mo | Anthropometry: height, weight, sitting height, blood pressure, Tanner stages |
| Every 6–12 mo | Laboratory: LH, FSH, E2/T, 25OH vitamin D |
| Every 1–2 y | Bone density using DXA Bone age on X-ray of the left hand (if clinically indicated) |

Adapted from Hembree *et al.* (118).

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone;

Table 8. Protocol Induction of Puberty

| |
|--------------------------------------------------------------------------------------------------------------------------------------|
| Induction of female puberty with oral 17β -estradiol, increasing the dose every 6 mo: |
| 5 $\mu\text{g}/\text{kg}/\text{d}$ |
| 10 $\mu\text{g}/\text{kg}/\text{d}$ |
| 15 $\mu\text{g}/\text{kg}/\text{d}$ |
| 20 $\mu\text{g}/\text{kg}/\text{d}$ |
| Adult dose = 2–6 mg/d |
| <i>In postpubertal transgender female adolescents, the dose of 17β-estradiol can be increased more rapidly:</i> |
| 1 mg/d for 6 mo |
| 2 mg/d |
| Induction of female puberty with transdermal 17β -estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d): |
| 6.25–12.5 $\mu\text{g}/24\text{ h}$ (cut 25- μg patch into quarters, then halves) |
| 25 $\mu\text{g}/24\text{ h}$ |
| 37.5 $\mu\text{g}/24\text{ h}$ |
| Adult dose = 50–200 $\mu\text{g}/24\text{ h}$ |
| <i>For alternatives once at adult dose, see Table 11.</i> |
| <i>Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).</i> |
| Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC): |
| 25 mg/ $\text{m}^2/2\text{ wk}$ (or alternatively, half this dose weekly, or double the dose every 4 wk) |
| 50 mg/ $\text{m}^2/2\text{ wk}$ |
| 75 mg/ $\text{m}^2/2\text{ wk}$ |
| 100 mg/ $\text{m}^2/2\text{ wk}$ |
| Adult dose = 100–200 mg every 2 wk |
| <i>In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:</i> |
| 75 mg/2 wk for 6 mo |
| 125 mg/2 wk |
| <i>For alternatives once at adult dose, see Table 11.</i> |
| <i>Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).</i> |

Adapted from Hembree et al. (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15 to 16 years (119), and in many countries 16-year-olds are legally competent with regard to medical decision making (120). However, others believe that although some capacities are generally achieved before age 16 years, other abilities (such as good risk

assessment) do not develop until well after 18 years (121). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures, such as most surgical procedures (121).

Currently available data from transgender adolescents support treatment with sex hormones starting at age 16 years (63, 122). However, some patients may incur potential risks by waiting until age 16 years. These include the potential risk to bone health if puberty is suppressed

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Table 9. Baseline and Follow-up Protocol During Induction of Puberty

| |
|--------------------------------------------------------------------------------------------------------------------|
| Every 3–6 mo |
| •Anthropometry: height, weight, sitting height, blood pressure, Tanner stages |
| Every 6–12 mo |
| •In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin D |
| •In transgender females: prolactin, estradiol, 25OH vitamin D |
| Every 1–2 y |
| •BMD using DXA |
| •Bone age on X-ray of the left hand (if clinically indicated) |
| <i>BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).</i> |
| <i>For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.</i> |

Adapted from Hembree et al. (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.

for 6 to 7 years before initiating sex hormones (e.g., if someone reached Tanner stage 2 at age 9-10 years old). Additionally, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age. However, only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents currently exist (63). Clearly, long-term studies are needed to determine the optimal age of sex hormone treatment in GD/gender-incongruent adolescents.

The MHP who has followed the adolescent during GnRH analog treatment plays an essential role in assessing whether the adolescent is eligible to start sex hormone therapy and capable of consenting to this treatment (Table 5). Support of the family/environment is essential. Prior to the start of sex hormones, clinicians should discuss the implications for fertility (see recommendation 1.5). Throughout pubertal induction, an MHP and a pediatric endocrinologist (or other clinician competent in the evaluation and induction of pubertal development) should monitor the adolescent. In addition to monitoring therapy, it is also important to pay attention to general adolescent health issues, including healthy life style choices, such as not smoking, contraception, and appropriate vaccinations (e.g., human papillomavirus).

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal adolescents with GD/gender incongruence as they use in other individuals with hypogonadism, carefully monitoring for desired and undesired effects (Table 8). In transgender female adolescents, transdermal 17 β -estradiol may be an alternative for oral 17 β -estradiol. It is increasingly used for pubertal induction in hypogonadal females. However, the absence of low-dose estrogen patches may be a problem. As a result, individuals may need to cut patches to size themselves to achieve appropriate dosing (123). In transgender male adolescents, clinicians can give testosterone injections intramuscularly or subcutaneously (124, 125).

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an

adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 "Hormonal Therapy for Transgender Adults").

Values and preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (128).

Remarks

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed. Adult height may be a concern in transgender adolescents. In a transgender female adolescent, clinicians may consider higher doses of estrogen or a more rapid tempo of dose escalation during pubertal induction. There are no established treatments yet to augment adult height in a transgender male adolescent with open epiphyses during pubertal induction. It is not uncommon for transgender adolescents to present for clinical services after having completed or nearly completed puberty. In such cases, induction of puberty with sex hormones can be done more rapidly (see Table 8). Additionally, an adult dose of testosterone in transgender male adolescents may suffice to suppress the gonadal axis without the need to use a separate agent. At the appropriate time, the multidisciplinary team should adequately prepare the adolescent for transition to adult care.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are (1) to reduce endogenous sex hormone levels, and thus reduce

the secondary sex characteristics of the individual's designated gender, and (2) to replace endogenous sex hormone levels consistent with the individual's gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is codetermined in collaboration with both the person pursuing transition and the health care providers. The treatment team should include a medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender incongruence and the mental health concerns of transition, and a primary care provider able to provide care appropriate for transgender individuals. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being (129, 130).

- 3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 I⊕⊕⊕○)
- 3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment (Table 10). (1 I⊕⊕⊕○)
- 3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 I⊕⊕○○)

Evidence

It is the responsibility of the treating clinician to confirm that the person fulfills criteria for treatment. The treating clinician should become familiar with the terms and criteria presented in Tables 1–5 and take a thorough history from the patient in collaboration with the other members of the treatment team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, risks, and benefits of treatment are well understood; and the desire for transition persists. They also need to discuss fertility preservation options (see recommendation 1.3) (67, 68).

Transgender males

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in transgender males (Appendix A) (113, 114, 131–134). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (135). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (this is dependent on the specific assay, but is typically 320 to 1000 ng/dL) (Table 11) (136). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see section 4.0 "Adverse Outcome Prevention and Long-Term Care") and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in transgender males results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness in those genetically predisposed, and increased sexual desire (137).

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen

Very high risk of adverse outcomes:

- Thromboembolic disease

Moderate risk of adverse outcomes:

- Macroprolactinoma
- Breast cancer
- Coronary artery disease
- Cerebrovascular disease
- Cholelithiasis
- Hypertriglyceridemia

Transgender male: testosterone

Very high risk of adverse outcomes:

- Erythrocytosis (hematocrit > 50%)

Moderate risk of adverse outcomes:

- Severe liver dysfunction (transaminases > threefold upper limit of normal)
- Coronary artery disease
- Cerebrovascular disease
- Hypertension
- Breast or uterine cancer

Table 11. Hormone Regimens in Transgender Persons

| | |
|---------------------------------------------------------------|-------------------------------------------------------|
| Transgender females ^a | |
| Estrogen | |
| Oral | |
| Estradiol | 2.0–6.0 mg/d |
| Transdermal | |
| Estradiol transdermal patch (New patch placed every 3–5 d) | 0.025–0.2 mg/d |
| Parenteral | |
| Estradiol valerate or cypionate | 5–30 mg IM every 2 wk 2–10 mg IM every week |
| Anti-androgens | |
| Spironolactone | 100–300 mg/d |
| Cyproterone acetate ^b | 25–50 mg/d |
| GnRH agonist | 3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly |
| Transgender males | |
| Testosterone | |
| Parenteral testosterone | |
| Testosterone enanthate or cypionate | 100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week |
| Testosterone undecanoate ^c | 1000 mg every 12 wk |
| Transdermal testosterone | |
| Testosterone gel 1.6% ^d | 50–100 mg/d |
| Testosterone transdermal patch | 2.5–7.5 mg/d |

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

^aEstrogens used with or without antiandrogens or GnRH agonist.

^bNot available in the United States.

^cOne thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

^dAvoid cutaneous transfer to other individuals.

In transgender males, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, cessation of menses (usually), and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (138). Clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Transgender females

The hormone regimen for transgender females is more complex than the transgender male regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for females (139). Most published clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range (21, 113, 114, 132–134, 139, 140).

Multiple adjunctive medications are available, such as progestins with antiandrogen activity and GnRH agonists (141). Spironolactone works by directly blocking androgens during their interaction with the androgen

receptor (114, 133, 142). It may also have estrogenic activity (143). Cyproterone acetate, a progestational compound with antiandrogenic properties (113, 132, 144), is widely used in Europe. 5α -Reductase inhibitors do not reduce testosterone levels and have adverse effects (145).

Dittrich *et al.* (141) reported that monthly doses of the GnRH agonist goserelin acetate in combination with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 60 transgender females. Leuprolide and transdermal estrogen were as effective as cyproterone and transdermal estrogen in a comparative retrospective study (146).

Patients can take estrogen as oral conjugated estrogens, oral 17 β -estradiol, or transdermal 17 β -estradiol. Among estrogen options, the increased risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically (134, 140, 141), which is why we specifically suggest that it not be used in any transgender treatment plan. Data distinguishing among other estrogen options are less well established although there is some thought that oral routes of administration are more thrombogenic due to the “first pass effect” than are transdermal and parenteral routes, and that the risk of thromboembolic events is dose-dependent. Injectable estrogen and sublingual

estrogen may benefit from avoiding the first pass effect, but they can result in more rapid peaks with greater overall periodicity and thus are more difficult to monitor (147, 148). However, there are no data demonstrating that increased periodicity is harmful otherwise.

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogen use. Clinicians should measure serum estradiol and serum testosterone and maintain them at the level for premenopausal females (100 to 200 pg/mL and <50 ng/dL, respectively). The transdermal preparations and injectable estradiol cypionate or valerate preparations may confer an advantage in older transgender females who may be at higher risk for thromboembolic disease (149).

Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (150).

Not all individuals with GD/gender incongruence seek treatment as described (e.g., male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (151). We need prospective studies to better understand treatment options for these persons.

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 I \oplus OOO)

Evidence

Transgender males

Physical changes that are expected to occur during the first 1 to 6 months of testosterone therapy include

cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice (152, 153), clitoromegaly, and male pattern hair loss (in some cases) (114, 144, 154, 155) (Table 12).

Transgender females

Physical changes that may occur in transgender females in the first 3 to 12 months of estrogen and anti-androgen therapy include decreased sexual desire, decreased spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, increased breast tissue growth, and redistribution of fat mass (114, 139, 149, 154, 155, 161) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (114, 139, 149, 155). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in transgender females has been studied (150), precise information about other changes induced by sex hormones is lacking (141). There is a great deal of variability among individuals, as evidenced during pubertal development. We all know that a major concern for transgender females is breast development. If we work with estrogens, the result will be often not what the transgender female expects.

Alternatively, there are transgender females who report an anecdotal improved breast development, mood, or sexual desire with the use of progestogens. However, there have been no well-designed studies of the role of progestogens in feminizing hormone regimens, so the question is still open.

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast

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Table 12. Masculinizing Effects in Transgender Males

| Effect | Onset | Maximum |
|--------------------------------|---------|----------------|
| Skin oiliness/acne | 1–6 mo | 1–2 y |
| Facial/body hair growth | 6–12 mo | 4–5 y |
| Scalp hair loss | 6–12 mo | — ^a |
| Increased muscle mass/strength | 6–12 mo | 2–5 y |
| Fat redistribution | 1–6 mo | 2–5 y |
| Cessation of menses | 1–6 mo | — ^b |
| Clitoral enlargement | 1–6 mo | 1–2 y |
| Vaginal atrophy | 1–6 mo | 1–2 y |
| Deepening of voice | 6–12 mo | 1–2 y |

Estimates represent clinical observations: Toorians *et al.* (149), Assche- man *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

^aPrevention and treatment as recommended for biological men.

^bMenorrhagia requires diagnosis and treatment by a gynecologist.

Table 13. Feminizing Effects in Transgender Females

| Effect | Onset | Maximum |
|--------------------------------------|----------|-------------------|
| Redistribution of body fat | 3–6 mo | 2–3 y |
| Decrease in muscle mass and strength | 3–6 mo | 1–2 y |
| Softening of skin/decreased oiliness | 3–6 mo | Unknown |
| Decreased sexual desire | 1–3 mo | 3–6 mo |
| Decreased spontaneous erections | 1–3 mo | 3–6 mo |
| Male sexual dysfunction | Variable | Variable |
| Breast growth | 3–6 mo | 2–3 y |
| Decreased testicular volume | 3–6 mo | 2–3 y |
| Decreased sperm production | Unknown | >3 y ^a |
| Decreased terminal hair growth | 6–12 mo | >3 y ^a |
| Scalp hair | Variable | — ^b |
| Voice changes | None | — ^c |

Estimates represent clinical observations: Toorians *et al.* (149), Asschelman *et al.* (156), Gooren *et al.* (157).

^aComplete removal of male sexual hair requires electrolysis or laser treatment or both.

^bFamilial scalp hair loss may occur if estrogens are stopped.

^cTreatment by speech pathologists for voice training is most effective.

development in transgender females is extremely sparse and based on the low quality of evidence. Current evidence does not indicate that progestogens enhance breast development in transgender females, nor does evidence prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions (162).

Values and preferences

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.*, breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone–induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender males and females confers many of the same risks associated with sex hormone replacement therapy in nontransgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (131, 139).

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every

3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 I⊕⊕○○)

Evidence

Pretreatment screening and appropriate regular medical monitoring are recommended for both transgender males and females during the endocrine transition and periodically thereafter (26, 155). Clinicians should monitor weight and blood pressure, conduct physical exams, and assess routine health questions, such as tobacco use, symptoms of depression, and risk of adverse events such as deep vein thrombosis/pulmonary embolism and other adverse effects of sex steroids.

Transgender males

Table 14 contains a standard monitoring plan for transgender males on testosterone therapy (154, 159). Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (135).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (163, 164). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (144, 165, 166).

Transgender females

Table 15 contains a standard monitoring plan for transgender females on estrogens, gonadotropin suppression, or antiandrogens (160). Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitor serum estradiol levels using laboratories participating in external quality control, as measurements of estradiol in blood can be very challenging (167).

VTE may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (161). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (149). The incidence decreased when clinicians stopped administering ethinyl estradiol (161). Thus, the use of synthetic estrogens and conjugated estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1 of 60 of transgender females treated with a GnRH analog and oral

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:^a
 - a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
 - b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
 - c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

^aAdapted from Lapaauw et al. (154) and Ott et al. (159).

estradiol (141). The patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase gene. In an Austrian gender clinic, administering gender-affirming hormones to 162 transgender females and 89 transgender males was not associated with VTE, despite an 8.0% and 5.6% incidence of thrombophilia (159). A more recent multinational study reported only 10 cases of VTE from a cohort of 1073 subjects (168). Thrombophilia screening of transgender persons initiating hormone treatment should be restricted to those with a personal or family history of VTE (159). Monitoring D-dimer levels during treatment is not recommended (169).

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 I⊕⊕○○)

Evidence

Estrogen therapy can increase the growth of pituitary lactotroph cells. There have been several reports of prolactinomas occurring after long-term, high-dose

estrogen therapy (170–173). Up to 20% of transgender females treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (156). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or discontinuation of cyproterone acetate (157, 174, 175).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and every 2 years thereafter. Given that only a few case studies reported prolactinomas, and prolactinomas were not reported in large cohorts of estrogen-treated persons, the risk is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in transgender females, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels (174).

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
 - a. Serum testosterone levels should be <50 ng/dL.
 - b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 I⊕O○)

Evidence

Transgender males

Administering testosterone to transgender males results in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol values (176–179). Studies of the effect of testosterone on insulin sensitivity have mixed results (178, 180). A randomized, open-label uncontrolled safety study of transgender males treated with testosterone undecanoate demonstrated no insulin resistance after 1 year (181, 182). Numerous studies have demonstrated the effects of sex hormone treatment on the cardiovascular system (160, 179, 183, 184). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185). A systematic review of the literature found that data were insufficient (due to very low-quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176). Clinicians should manage cardiovascular risk factors as they emerge according to established guidelines (186).

Transgender females

A prospective study of transgender females found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (178). However, increased weight, blood pressure, and markers of insulin resistance attenuated these favorable lipid changes. In a meta-analysis, only serum triglycerides were higher at ≥ 24 months without changes in other parameters (187). The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).

Thus, there is limited evidence to determine whether estrogen is protective or detrimental on lipid and glucose metabolism in transgender females (176). With aging, there is usually an increase of body weight. Therefore, as with nontransgender individuals, clinicians should

monitor and manage glucose and lipid metabolism and blood pressure regularly according to established guidelines (186).

4.4. We recommend that clinicians obtain BMD measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 I⊕O○)

Evidence

Transgender males

Baseline bone mineral measurements in transgender males are generally in the expected range for their pre-treatment gender (188). However, adequate dosing of testosterone is important to maintain bone mass in transgender males (189, 190). In one study (190), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels in the normal range may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol, both systemically and locally in the bone.

Transgender females

A baseline study of BMD reported T scores less than -2.5 in 16% of transgender females (191). In aging males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (192, 193) and is more important for peak bone mass (194). Estrogen preserves BMD in transgender females who continue on estrogen and antiandrogen therapies (188, 190, 191, 195, 196).

Fracture data in transgender males and females are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss. There have been no studies to determine whether clinicians should use the sex assigned at birth or affirmed gender for assessing osteoporosis (e.g., when using the FRAX tool). Although some researchers use the sex assigned at birth (with the assumption that bone mass has usually peaked for transgender people who initiate hormones in early adulthood), this should be assessed on a case-by-case basis until there are more data available. This assumption will be further complicated by the increasing prevalence of transgender people who undergo hormonal transition at a pubertal age or soon after puberty. Sex for comparison within risk assessment tools may be based on the age at which hormones were initiated and the length of exposure to hormones. In some cases, it may be

reasonable to assess risk using both the male and female calculators and using an intermediate value. Because all subjects underwent normal pubertal development, with known effects on bone size, reference values for birth sex were used for all participants (154).

- 4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for those designated female at birth. (2 I⊕OO)
- 4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 I⊕OOO)

Evidence

Studies have reported a few cases of breast cancer in transgender females (197–200). A Dutch study of 1800 transgender females followed for a mean of 15 years (range of 1–30 years) found one case of breast cancer. The Women's Health Initiative study reported that females taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with females taking placebo (137).

In transgender males, a large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven breast cancers (194). The authors reported that this was not above the expected rate of breast cancers in cisgender females in this cohort. Furthermore, they did report one breast cancer that developed in a transgender male patient after mastectomy, supporting the fact that breast cancer can occur even after mastectomy. Indeed, there have been case reports of breast cancer developing in subareolar tissue in transgender males, which occurred after mastectomy (201, 202).

Women with primary hypogonadism (Turner syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (203, 204). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20 to 30 years). We need long-term studies to determine the actual risk, as well as the role of screening mammograms. Regular examinations and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen deprivation therapy (205). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (206). Although van Kesteren *et al.* (207) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostates of

transgender females, studies have reported cases of benign prostatic hyperplasia in transgender females treated with estrogens for 20 to 25 years (208, 209). Studies have also reported a few cases of prostate carcinoma in transgender females (210–214).

Transgender females may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for transgender females who transitioned after age 20 years to have annual screening digital rectal examinations after age 50 years and prostate-specific antigen tests consistent with U.S. Preventive Services Task Force Guidelines (215).

- 4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

Evidence

Although aromatization of testosterone to estradiol in transgender males has been suggested as a risk factor for endometrial cancer (216), no cases have been reported. When transgender males undergo hysterectomy, the uterus is small and there is endometrial atrophy (217, 218). Studies have reported cases of ovarian cancer (219, 220). Although there is limited evidence for increased risk of reproductive tract cancers in transgender males, health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer (221).

Values

Given the discomfort that transgender males experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. Additionally, in certain countries, the approval required to change the sex in a birth certificate for transgender males may be dependent on having a complete hysterectomy. Clinicians should help patients research nonmedical administrative criteria and

provide counseling. If individuals decide not to undergo hysterectomy, screening for cervical cancer is the same as all other females.

5.0 Surgery for Sex Reassignment and Gender Confirmation

For many transgender adults, genital gender-affirming surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. The type of surgery falls into two main categories: (1) those that directly affect fertility and (2) those that do not. Those that change fertility (previously called sex reassignment surgery) include genital surgery to remove the penis and gonads in the male and removal of the uterus and gonads in the female. The surgeries that effect fertility are often governed by the legal system of the state or country in which they are performed. Other gender-conforming surgeries that do not directly affect fertility are not so tightly governed.

Gender-affirming surgical techniques have improved markedly during the past 10 years. Reconstructive genital surgery that preserves neurologic sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (187). Additionally, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (130, 144) (Table 16).

Surgery that affects fertility is irreversible. The World Professional Association for Transgender Health Standards of Care (222) emphasizes that the “threshold of 18 should not be seen as an indication in itself for active intervention.” If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then the individual should not be referred for surgery (223, 224).

Gender-affirming genital surgeries for transgender females that affect fertility include gonadectomy, penectomy, and creation of a neovagina (225, 226). Surgeons often invert the skin of the penis to form the wall of the vagina, and several literatures reviews have

reported on outcomes (227). Sometimes there is inadequate tissue to form a full neovagina, so clinicians have revisited using intestine and found it to be successful (87, 228, 229). Some newer vaginoplasty techniques may involve autologous oral epithelial cells (230, 231).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also creating a sensate pedicled-spot adding a G spot to the neovagina to increase sensation (232). Most recently, plastic surgeons have developed techniques to fashion labia minora. To further complete the feminization, uterine transplants have been proposed and even attempted (233).

Neovaginal prolapse, rectovaginal fistula, delayed healing, vaginal stenosis, and other complications do sometimes occur (234, 235). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsiveness and other aspects of sexual function are usually preserved following genital gender-affirming surgery (236, 237).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of transgender males (152, 238). No studies have compared the effectiveness of speech therapy, laryngeal surgery, or combined treatment.

Breast surgery is a good example of gender-confirming surgery that does not affect fertility. In all females, breast size exhibits a very broad spectrum. For transgender females to make the best informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, because the breasts continue to grow during that time (141, 155).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (e.g., cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

laser treatments. Other feminizing surgeries, such as that to feminize the face, are now becoming more popular (239–241).

In transgender males, clinicians usually delay gender-affirming genital surgeries until after a few years of androgen therapy. Those surgeries that affect fertility in this group include oophorectomy, vaginectomy, and complete hysterectomy. Surgeons can safely perform them vaginally with laparoscopy. These are sometimes done in conjunction with the creation of a neopenis. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (242, 243). Radial forearm flap seems to be the most satisfactory procedure (228, 244). Other flaps also exist (245). Surgeons can make neopenile erections possible by reinervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (246, 247), but results are inconsistent (248). Surgeons can also stiffen the penis by imbedding some mechanical device (*e.g.*, a rod or some inflatable apparatus) (249, 250). Because of these limitations, the creation of a neopenis has often been less than satisfactory. Recently, penis transplants are being proposed (233).

In fact, most transgender males do not have any external genital surgery because of the lack of access, high cost, and significant potential complications. Some choose a metoidioplasty that brings forward the clitoris, thereby allowing them to void in a standing position without wetting themselves (251, 252). Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (253).

The most important masculinizing surgery for the transgender male is mastectomy, and it does not affect fertility. Breast size only partially regresses with androgen therapy (155). In adults, discussions about mastectomy usually take place after androgen therapy has started. Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy 2 years after they begin androgen therapy and before age 18 years. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (254, 255). These often involve chest contouring (256). Mastectomy is often necessary for living comfortably in the new gender (256).

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically

necessary and would benefit the patient's overall health and/or well-being. (1 $\text{I} \oplus \text{OO}$)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 $\text{I} \oplus \text{OO}$)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 $\text{I} \oplus \text{OO}$)

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 $\text{I} \oplus \text{OO}$)

Evidence

Owing to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. However, one systematic review including a large numbers of studies reported satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (257). For transgender males, the outcomes are less certain. However, the problems are now better understood (258). Several postoperative studies report significant long-term psychological and psychiatric pathology (259–261). One study showed satisfaction with breasts, genitals, and femininity increased significantly and showed the importance of surgical treatment as a key therapeutic option for transgender females (262). Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of

causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263). Reversal surgery in regretful male-to-female transsexuals after sexual reassignment surgery represents a complex, multistage procedure with satisfactory outcomes. Further insight into the characteristics of persons who regret their decision postoperatively would facilitate better future selection of applicants eligible for sexual reassignment surgery. We need more studies with appropriate controls that examine long-term quality of life, psychosocial outcomes, and psychiatric outcomes to determine the long-term benefits of surgical treatment.

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies criteria for gender-affirming surgery (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (176). For this reason, the surgeon and the hormone-prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery. One study suggests that preoperative factors (such as compliance) are less important for patient satisfaction than are the physical postoperative results (56). However, other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not achieve treatment goals (264) and experience higher rates of postoperative infections and other complications (265, 266). It is also important that the person requesting surgery feels comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (223).

An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.

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Correspondence and Reprint Requests: The Endocrine Society, 2055 L Street NW, Suite 600, Washington, DC 20036. E-mail: publications@endocrine.org; Phone: 202971-3636.

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References

1. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW, Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490.
2. Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab*. 2008;93(3):666–673.
3. Bullough VL. Transsexualism in history. *Arch Sex Behav*. 1975; 4(5):561–571.
4. Benjamin H. The transsexual phenomenon. *Trans N Y Acad Sci*. 1967;29(4):428–430.
5. Meyerowitz J. *How Sex Changed: A History of Transsexuality in the United States*. Cambridge, MA: Harvard University Press; 2002.
6. Hirschfeld M. *Was muss das Volk vom Dritten Geschlecht wissen*. Verlag Max Spohr, Leipzig; 1901.
7. Fisk NM. Editorial: Gender dysphoria syndrome—the conceptualization that liberalizes indications for total gender re-orientation and implies a broadly based multi-dimensional rehabilitative regimen. *West J Med*. 1974;120(5):386–391.
8. Diamond L. Transgender experience and identity. In: Schwartz SJ, Luyckx K, Vignoles VL, eds. *Handbook of Identity Theory and Research*. New York, NY: Springer; 2011:629–647.
9. Queen C, Schimel L, eds. *PoMoSexuals: Challenging Assumptions About Gender and Sexuality*. San Francisco, CA: Cleis Press; 1997.
10. Case LK, Ramachandran VS. Alternating gender incongruity: a new neuropsychiatric syndrome providing insight into the dynamic plasticity of brain-sex. *Med Hypotheses*. 2012;78(5): 626–631.
11. Johnson TW, Wassersug RJ. Gender identity disorder outside the binary: when gender identity disorder-not otherwise specified is not good enough. *Arch Sex Behav*. 2010;39(3):597–598.
12. Wibowo E, Wassersug R, Warkentin K, Walker L, Robinson J, Brotto L, Johnson T. Impact of androgen deprivation therapy on sexual function: a response. *Asian J Androl*. 2012;14(5):793–794.
13. Pasqueno V. 7 countries giving transgender people fundamental rights the U.S. still won't. 2014. Available at: <https://mic.com/articles/87149/7-countries-giving-transgender-people-fundamental-rights-the-u-s-still-won-t>. Accessed 26 August 2016.
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association Publishing.
15. Drescher J, Cohen-Kettenis P, Winter S. Minding the body: situating gender identity diagnoses in the ICD-11. *Int Rev Psychiatry*. 2012;24(6):568–577.
16. World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people. Available at: http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926. Accessed 1 September 2017.
17. Kreukels BP, Haraldsen IR, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis PT. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry*. 2012;27(6):445–450.
18. Dekker MJ, Wierckx K, Van Caenegem E, Klaver M, Kreukels BP, Elaut E, Fisher AD, van Trotsenburg MA, Schreiner T, den Heijer M, T'Sjoen G. A European network for the investigation of gender incongruence: endocrine part. *J Sex Med*. 2016;13(6):994–999.
19. Ruble DN, Martin CL, Berenbaum SA. Gender development. In: Damon WL, Lerner RM, Eisenberg N, eds. *Handbook of Child Psychology: Social, Emotional, and Personality Development*. Vol. 3. 6th ed. New York, NY: Wiley; 2006:858–931.
20. Steensma TD, Kreukels BP, de Vries AL, Cohen-Kettenis PT. Gender identity development in adolescence. *Horm Behav*. 2013; 64(2):288–297.
21. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrinol Metab*. 2014;99(12): 4379–4389.
22. Saraswat A, Weinand JD, Safer JD. Evidence supporting the biologic nature of gender identity. *Endocr Pract*. 2015;21(2): 199–204.
23. Gooren L. The biology of human psychosexual differentiation. *Horm Behav*. 2006;50(4):589–601.
24. Berenbaum SA, Meyer-Bahlburg HF. Gender development and sexuality in disorders of sex development. *Horm Metab Res*. 2015; 47(5):361–366.
25. Dessens AB, Slijper FME, Drop SLS. Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Arch Sex Behav*. 2005;34(4):389–397.
26. Meyer-Bahlburg HFL, Dolezal C, Baker SW, Ehrhardt AA, New MI. Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. *Arch Sex Behav*. 2006; 35(6):667–684.
27. Frisén L, Nordenström A, Falhammar H, Filipsson H, Holmdahl G, Janson PO, Thorén M, Hagenfeldt K, Möller A, Nordenkjöld A. Gender role behavior, sexuality, and psychosocial adaptation in women with congenital adrenal hyperplasia due to CYP21A2 deficiency. *J Clin Endocrinol Metab*. 2009;94(9):3432–3439.
28. Meyer-Bahlburg HFL, Dolezal C, Baker SW, Carlson AD, Obeid JS, New MI. Prenatal androgenization affects gender-related behavior but not gender identity in 5–12-year-old girls with congenital adrenal hyperplasia. *Arch Sex Behav*. 2004;33(2):97–104.
29. Cohen-Kettenis PT. Gender change in 46,XY persons with 5α-reductase-2 deficiency and 17β-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005;34(4):399–410.
30. Reiner WG, Gearhart JP. Discordant sexual identity in some genetic males with cloacal exstrophy assigned to female sex at birth. *N Engl J Med*. 2004;350(4):333–341.
31. Meyer-Bahlburg HFL. Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. *Arch Sex Behav*. 2005;34(4):423–438.
32. Coolidge FL, Thede LL, Young SE. The heritability of gender identity disorder in a child and adolescent twin sample. *Behav Genet*. 2002;32(4):251–257.
33. Heylens G, De Cuypere G, Zucker KJ, Schelfaut C, Elaut E, Vanden Bossche H, De Baere E, T'Sjoen G. Gender identity disorder in twins: a review of the case report literature. *J Sex Med*. 2012;9(3):751–757.
34. Fernández R, Esteva I, Gómez-Gil E, Rumbo T, Almaraz MC, Roda E, Haro-Mora J-J, Guillamón A, Pásaro E. Association study of ERβ, AR, and CYP19A1 genes and MtF transsexualism. *J Sex Med*. 2014;11(12):2986–2994.
35. Henningsson S, Westberg L, Nilsson S, Lundström B, Ekselius L, Bodlund O, Lindström E, Hellstrand M, Rosmond R, Eriksson E, Landén M. Sex steroid-related genes and male-to-female transsexualism. *Psychoneuroendocrinology*. 2005;30(7):657–664.
36. Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry*. 2009;65(1):93–96.
37. Lombardo F, Toselli L, Grassetti D, Paoli D, Masciandaro P, Valentini F, Lenzi A, Gandini L. Hormone and genetic study in

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male to female transsexual patients. *J Endocrinol Invest.* 2013; 36(8):550–557.

38. Ujike H, Otani K, Nakatsuka M, Ishii K, Sasaki A, Oishi T, Sato T, Okahisa Y, Matsumoto Y, Namba Y, Kimata Y, Kuroda S. Association study of gender identity disorder and sex hormone-related genes. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009;33(7):1241–1244.

39. Kreukels BP, Guillamon A. Neuroimaging studies in people with gender incongruence. *Int Rev Psychiatry.* 2016;28(1): 120–128.

40. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry.* 2011;16(4):499–516.

41. Wallien MSC, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. *J Am Acad Child Adolesc Psychiatry.* 2008;47(12):1413–1423.

42. Steensma TD, McGuire JK, Kreukels BPC, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry.* 2013;52(6):582–590.

43. Cohen-Kettenis PT, Owen A, Kajser VG, Bradley SJ, Zucker KJ. Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: a cross-national, cross-clinic comparative analysis. *J Abnorm Child Psychol.* 2003;31(1):41–53.

44. Dhejne C, Van Vlerken R, Heylens G, Arcelus J. Mental health and gender dysphoria: a review of the literature. *Int Rev Psychiatry.* 2016;28(1):44–57.

45. Pasterski V, Gilligan L, Curtis R. Traits of autism spectrum disorders in adults with gender dysphoria. *Arch Sex Behav.* 2014; 43(2):387–393.

46. Spack NP, Edwards-Leeper L, Feldman HA, Leibowitz S, Mandel F, Diamond DA, Vance SR. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics.* 2012;129(3):418–425.

47. Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Factors predicting psychiatric co-morbidity in gender-dysphoric adults. *Psychiatry Res.* 2012;200(2–3):469–474.

48. VanderLaan DP, Leef JH, Wood H, Hughes SK, Zucker KJ. Autism spectrum disorder risk factors and autistic traits in gender dysphoric children. *J Autism Dev Disord.* 2015;45(6):1742–1750.

49. de Vries ALC, Doreleijers TAH, Steensma TD, Cohen-Kettenis PT. Psychiatric comorbidity in gender dysphoric adolescents. *J Child Psychol Psychiatry.* 2011;52(11):1195–1202.

50. de Vries ALC, Noens ILJ, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. *J Autism Dev Disord.* 2010; 40(8):930–936.

51. Wallien MSC, Swaab H, Cohen-Kettenis PT. Psychiatric comorbidity among children with gender identity disorder. *J Am Acad Child Adolesc Psychiatry.* 2007;46(10):1307–1314.

52. Kuiper AJ, Cohen-Kettenis PT. Gender role reversal among postoperative transsexuals. Available at: <https://www.atria.nl/ezines/web/JJT97-03/numbers/symposium/jjtco502.htm>. Accessed 26 August 2016.

53. Landén M, Wålinder J, Hamberg G, Lundström B. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand.* 1998; 97(4):284–289.

54. Olsson S-E, Möller A. Regret after sex reassignment surgery in a male-to-female transsexual: a long-term follow-up. *Arch Sex Behav.* 2006;35(4):501–506.

55. Pfäfflin F, Junge A, eds. *Geschlechtsumwandlung: Abhandlungen zur Transsexualität.* Stuttgart, Germany: Schattauer; 1992.

56. Lawrence AA. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav.* 2003;32(4):299–315.

57. Cohen-Kettenis PT, Pfäfflin F. *Transgenderism and Intersexuality in Childhood and Adolescence: Making Choices.* Thousand Oaks, CA: SAGE Publications; 2003.

58. Di Ceglie D, Freedman D, McPherson S, Richardson P. Children and adolescents referred to a specialist gender identity development service: clinical features and demographic characteristics. Available at: https://www.researchgate.net/publication/276061306_Children_and_Adolescents_Referred_to_a_Specialist_Gender_Identity_Development_Service_Clinical_Features_and_Demographic_Characteristics. Accessed 20 July 2017.

59. Gijs L, Brewaeys A. Surgical treatment of gender dysphoria in adults and adolescents: recent developments, effectiveness, and challenges. *Annu Rev Sex Res.* 2007;18:178–224.

60. Cohen-Kettenis PT, van Goozen SHM. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry.* 1997;36(2):263–271.

61. Smith YLS, van Goozen SHM, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry.* 2001;40(4):472–481.

62. Smith YLS, Van Goozen SHM, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med.* 2005;35(1):89–99.

63. de Vries ALC, McGuire JK, Steensma TD, Wagenaar ECF, Doreleijers TAH, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics.* 2014;134(4):696–704.

64. Cole CM, O'Boyle M, Emory LE, Meyer WJ III. Comorbidity of gender dysphoria and other major psychiatric diagnoses. *Arch Sex Behav.* 1997;26(1):13–26.

65. Cohen-Kettenis PT, Schagen SEE, Steensma TD, de Vries ALC, Delemarre-van de Waal HA. Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up. *Arch Sex Behav.* 2011; 40(4):843–847.

66. First MB. Desire for amputation of a limb: paraphilia, psychosis, or a new type of identity disorder. *Psychol Med.* 2005;35(6): 919–928.

67. Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedecker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. *Hum Reprod.* 2012;27(2):483–487.

68. Wierckx K, Stuyver I, Weyers S, Hamada A, Agarwal A, De Sutter P, T'Sjoen G. Sperm freezing in transsexual women. *Arch Sex Behav.* 2012;41(5):1069–1071.

69. Bertelloni S, Baroncelli GI, Ferdeghini M, Menchini-Fabris F, Saggese G. Final height, gonadal function and bone mineral density of adolescent males with central precocious puberty after therapy with gonadotropin-releasing hormone analogues. *Eur J Pediatr.* 2000;159(5):369–374.

70. Büchter D, Behre HM, Kliesch S, Nieschlag E. Pulsatile GnRH or human chorionic gonadotropin/human menopausal gonadotropin as effective treatment for men with hypogonadotropic hypogonadism: a review of 42 cases. *Eur J Endocrinol.* 1998; 139(3):298–303.

71. Liu PY, Turner L, Rushford D, McDonald J, Baker HW, Conway AJ, Handelman DJ. Efficacy and safety of recombinant human follicle stimulating hormone (Gonal-F) with urinary human chorionic gonadotrophin for induction of spermatogenesis and fertility in gonadotrophin-deficient men. *Hum Reprod.* 1999; 14(6):1540–1545.

72. Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. *J Clin Endocrinol Metab.* 2008;93(1):190–195.

73. Magiakou MA, Manousaki D, Papadaki M, Hadjidakis D, Levidou G, Vakaki M, Papaefstathiou A, Lalioti N, Kanakagantenbein C, Piaditis G, Chrousos GP, Dacou-Voutetakis C. The

efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. *J Clin Endocrinol Metab.* 2010;95(1):109–117.

74. Baba T, Endo T, Honnma H, Kitajima Y, Hayashi T, Ikeda H, Masumori N, Kamiya H, Moriwaka O, Saito T. Association between polycystic ovary syndrome and female-to-male transsexuality. *Hum Reprod.* 2007;22(4):1011–1016.
75. Spinder T, Spijkstra JJ, van den Tweel JG, Burger CW, van Kessel H, Hompes PGA, Gooren LJG. The effects of long term testosterone administration on pulsatile luteinizing hormone secretion and on ovarian histology in eugonadal female to male transsexual subjects. *J Clin Endocrinol Metab.* 1989;69(1):151–157.
76. Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T. Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *J Sex Med.* 2011;8(6):1686–1693.
77. Vujošić S, Popović S, Sbutega-Milosević G, Djordjević M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. *J Sex Med.* 2009;6(4):1018–1023.
78. Ikeda K, Baba T, Noguchi H, Nagasawa K, Endo T, Kiya T, Saito T. Excessive androgen exposure in female-to-male transsexual persons of reproductive age induces hyperplasia of the ovarian cortex and stroma but not polycystic ovary morphology. *Hum Reprod.* 2013;28(2):453–461.
79. Trebay G. He's pregnant. You're speechless. New York Times. 22 June 2008.
80. Light AD, Obedin-Maliver J, Sevelius JM, Kerns JL. Transgender men who experienced pregnancy after female-to-male gender transitioning. *Obstet Gynecol.* 2014;124(6):1120–1127.
81. De Sutter P. Donor inseminations in partners of female-to-male transsexuals: should the question be asked? *Reprod Biomed Online.* 2003;6(3):382, author reply 282–283.
82. De Roo C, Tillemans K, T'Sjoen G, De Sutter P. Fertility options in transgender people. *Int Rev Psychiatry.* 2016;28(1):112–119.
83. Wennink JMB, Delemarre-van de Waal HA, Schoemaker R, Schoemaker H, Schoemaker J. Luteinizing hormone and follicle stimulating hormone secretion patterns in boys throughout puberty measured using highly sensitive immunoradiometric assays. *Clin Endocrinol (Oxf).* 1989;31(5):551–564.
84. Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJG. The treatment of adolescent transsexuals: changing insights. *J Sex Med.* 2008;5(8):1892–1897.
85. Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol.* 2006;155:S131–S137.
86. de Vries ALC, Steensma TD, Doreleijers TAH, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med.* 2011;8(8):2276–2283.
87. Bouman MB, van Zeeijl MCT, Buncamper ME, Meijerink WJHJ, van Bodegraven AA, Mullender MG. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. *J Sex Med.* 2014;11(7):1835–1847.
88. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Antoniazzi F, Berenbaum S, Bourguignon JP, Chrousos GP, Coste J, Deal S, de Vries L, Foster C, Heger S, Holland J, Jahnukainen K, Juul A, Kaplowitz P, Lahlou N, Lee MM, Lee P, Merke DP, Neely EK, Oostdijk W, Phillip M, Rosenfield RL, Shulman D, Styne D, Tauber M, Wit JM; ESPE-LWPES GnRH Analogs Consensus Conference Group. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics.* 2009;123(4):e752–e762.
89. Roth CL, Brendel L, Rückert C, Hartmann K. Antagonistic and agonistic GnRH analogue treatment of precocious puberty: tracking gonadotropin concentrations in urine. *Horm Res.* 2005;63(5):257–262.
90. Roth C. Therapeutic potential of GnRH antagonists in the treatment of precocious puberty. *Expert Opin Investig Drugs.* 2002;11(9):1253–1259.
91. Turomo T. Treatment of central precocious puberty. *Expert Opin Investig Drugs.* 2006;15(5):495–505.
92. Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. *J Sex Med.* 2016;13(7):1125–1132.
93. Manasco PK, Pescovitz OH, Feuillan PP, Hench KD, Barnes KM, Jones J, Hill SC, Loriaux DL, Cutler GB, Jr. Resumption of puberty after long term luteinizing hormone-releasing hormone agonist treatment of central precocious puberty. *J Clin Endocrinol Metab.* 1988;67(2):368–372.
94. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab.* 2015;100(2):E270–E275.
95. Finkelstein JS, Klibanski A, Neer RM. A longitudinal evaluation of bone mineral density in adult men with histories of delayed puberty. *J Clin Endocrinol Metab.* 1996;81(3):1152–1155.
96. Bertelloni S, Baroncelli GI, Ferdegiani M, Perri G, Saggese G. Normal volumetric bone mineral density and bone turnover in young men with histories of constitutional delay of puberty. *J Clin Endocrinol Metab.* 1998;83(12):4280–4283.
97. Darelid A, Ohlsson C, Nilsson M, Kindblom JM, Mellström D, Lorentzon M. Catch up in bone acquisition in young adult men with late normal puberty. *J Bone Miner Res.* 2012;27(10):2198–2207.
98. Mirtan D, Lee S, Miller E, Perez RC, Basler JW, Bruder JM. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. *J Clin Endocrinol Metab.* 2002;87(8):3656–3661.
99. Saggese G, Bertelloni S, Baroncelli GI, Battini R, Franchi G. Reduction of bone density: an effect of gonadotropin releasing hormone analogue treatment in central precocious puberty. *Eur J Pediatr.* 1993;152(9):717–720.
100. Neely EK, Bachrach LK, Hintz RL, Habiby RL, Slemenda CW, Feezle L, Pescovitz OH. Bone mineral density during treatment of central precocious puberty. *J Pediatr.* 1995;127(5):819–822.
101. Bertelloni S, Baroncelli GI, Sorrentino MC, Perri G, Saggese G. Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *Eur J Pediatr.* 1998;157(5):363–367.
102. Thornton P, Silverman LA, Geffner ME, Neely EK, Gould E, Danoff TM. Review of outcomes after cessation of gonadotropin-releasing hormone agonist treatment of girls with precocious puberty. *Pediatr Endocrinol Rev.* 2014;11(3):306–317.
103. Lem AJ, van der Kaay DC, Hokken-Koelega AC. Bone mineral density and body composition in short children born SGA during growth hormone and gonadotropin releasing hormone analog treatment. *J Clin Endocrinol Metab.* 2013;98(1):77–86.
104. Antoniazzi F, Zamboni G, Bertoldo F, Lauriola S, Mengarda F, Pietrobelli A, Tatò L. Bone mass at final height in precocious puberty after gonadotropin-releasing hormone agonist with and without calcium supplementation. *J Clin Endocrinol Metab.* 2003;88(3):1096–1101.
105. Calcaterra V, Mannarino S, Corana G, Codazzi AC, Mazzola A, Brambilla P, Larizza D. Hypertension during therapy with triptorelin in a girl with precocious puberty. *Indian J Pediatr.* 2013;80(10):884–885.
106. Siomou E, Kosmeri C, Pavlou M, Vlahos AP, Argyropoulou MI, Siamopoulou A. Arterial hypertension during treatment with triptorelin in a child with Williams-Beuren syndrome. *Pediatr Nephrol.* 2014;29(9):1633–1636.
107. Staphorsius AS, Kreukels BPC, Cohen-Kettenis PT, Veltman DJ, Burke SM, Schagen SEE, Wouters FM, Delemarre-van de Waal

HA, Bakker J. Puberty suppression and executive functioning: an fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology*. 2015;56:190–199.

108. Hough D, Bellingham M, Haraldsen IR, McLaughlin M, Rennie M, Robinson JE, Solbakk AK, Evans NP. Spatial memory is impaired by peripubertal GnRH agonist treatment and testosterone replacement in sheep. *Psychoneuroendocrinology*. 2017; 75:173–182.

109. Collipp PJ, Kaplan SA, Boyle DC, Plachte F, Kogut MD. Constitutional Isosexual Precocious Puberty. *Am J Dis Child.* 1964; 108:399–405.

110. Hahn HB, Jr, Hayles AB, Albert A. Medroxyprogesterone and constitutional precocious puberty. *Mayo Clin Proc.* 1964;39: 182–190.

111. Kaplan SA, Ling SM, Irani NG. Idiopathic isosexual precocity. *Am J Dis Child.* 1968;116(6):591–598.

112. Schoen EJ. Treatment of idiopathic precocious puberty in boys. *J Clin Endocrinol Metab.* 1966;26(4):363–370.

113. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res.* 2005;64(Suppl 2):31–36.

114. Moore E, Wisniewski A, Dobs A. Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. *J Clin Endocrinol Metab.* 2003;88(8):3467–3473.

115. Krueger RB, Hembree W, Hill M. Prescription of medroxyprogesterone acetate to a patient with pedophilia, resulting in Cushing's syndrome and adrenal insufficiency. *Sex Abuse.* 2006; 18(2):227–228.

116. Lynch MM, Khandheria MM, Meyer WJ. Retrospective study of the management of childhood and adolescent gender identity disorder using medroxyprogesterone acetate. *Int J Transgenderism.* 2015;16:201–208.

117. Tack LJW, Craen M, Dhondt K, Vanden Bossche H, Laridaen J, Cools M. Consecutive lystestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis. *Biol Sex Differ.* 2016;7:14.

118. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94(9):3132–3154.

119. Mann L, Harmoni R, Power C. Adolescent decision-making: the development of competence. *J Adolesc.* 1989;12(3):265–278.

120. Stultiëns L, Goffin T, Barry P, Dierickx K, Nys H. Minors and informed consent: a comparative approach. *Eur J Health Law.* 2007;14(1):21–46.

121. Arshagouni P. "But I'm an adult now ... sort of". Adolescent consent in health care decision-making and the adolescent brain. Available at: <http://digitalcommons.law.umaryland.edu/cgi/viewcontent.cgi?article=1124&context=jhclp>. Accessed 25 June 2017.

122. NHS. Prescribing of cross-sex hormones as part of the gender identity development service for children and adolescents. Available at: <https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/08/clinical-com-pol-16046.pdf>. Accessed 14 June 2017.

123. Ankarberg-Lindgren C, Kriström B, Norjavaara E. Physiological estrogen replacement therapy for puberty induction in girls: a clinical observational study. *Horm Res Paediatr.* 2014;81(4): 239–244.

124. Olson J, Schrager SM, Clark LF, Dunlap SL, Belzer M. Subcutaneous testosterone: an effective delivery mechanism for masculinizing young transgender men. *LGBT Health.* 2014;1(3): 165–167.

125. Spratt DI, Stewart I, Savage C, Craig W, Spack NP, Chandler DW, Spratt LV, Eimicke T, Olshan JS. Subcutaneous injection of testosterone is an effective and preferred alternative to intramuscular injection: demonstration in female-to-male transgender patients. *J Clin Endocrinol Metab.* 2017. doi:10.1210/jc.2017-00359

126. Eisenegger C, von Eckardstein A, Fehr E, von Eckardstein S. Pharmacokinetics of testosterone and estradiol gel preparations in healthy young men. *Psychoneuroendocrinology.* 2013;38(2): 171–178.

127. de Ronde W, ten Kerve J, Woerdeman J, Kaufman J-M, de Jong FH. Effects of oestradiol on gonadotrophin levels in normal and castrated men. *Clin Endocrinol (Oxf).* 2009;71(6):874–879.

128. Money J, Ehrhardt A. Man & woman, boy & girl: differentiation and dimorphism of gender identity from conception to maturity. Baltimore, MD: Johns Hopkins University Press; 1972:202–206.

129. Heylens G, Verroken C, De Cock S, T'Soën G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med.* 2014;11(1):119–126.

130. Costa R, Colizzi M. The effect of cross-sex hormonal treatment on gender dysphoria individuals' mental health: a systematic review. *Neuropsychiatr Dis Treat.* 2016;12:1953–1966.

131. Gooren LJG, Giltay EJ. Review of studies of androgen treatment of female-to-male transsexuals: effects and risks of administration of androgens to females. *J Sex Med.* 2008;5(4):765–776.

132. Levy A, Crown A, Reid R. Endocrine intervention for transsexuals. *Clin Endocrinol (Oxf).* 2003;59(4):409–418.

133. Tangpricha V, Ducharme SH, Barber TW, Chipkin SR. Endocrinologic treatment of gender identity disorders. *Endocr Pract.* 2003;9(1):12–21.

134. Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf).* 2015;83(5):597–606.

135. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2006;91(6): 1995–2010.

136. Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola MC. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med.* 2014;11(12):3002–3011.

137. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291(14):1701–1712.

138. Dickersin K, Munro MG, Clark M, Langenberg P, Scherer R, Frick K, Zhu Q, Hallock L, Nichols J, Yalcinkaya TM; Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding (STOP-DUB) Research Group. Hysterectomy compared with endometrial ablation for dysfunctional uterine bleeding: a randomized controlled trial. *Obstet Gynecol.* 2007;110(6): 1279–1289.

139. Gooren LJ, Giltay EJ, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab.* 2008;93(1):19–25.

140. Prior JC, Vigna YM, Watson D. Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. *Arch Sex Behav.* 1989;18(1):49–57.

141. Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann MW, Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes.* 2005;113(10):586–592.

142. Stripp B, Taylor AA, Bartter FC, Gillette JR, Loriaux DL, Easley R, Menard RH. Effect of spironolactone on sex hormones in man. *J Clin Endocrinol Metab*. 1975;41(4):777–781.

143. Levy J, Bursshell A, Marbach M, Aflalo L, Glick SM. Interaction of spironolactone with oestradiol receptors in cytosol. *J Endocrinol*. 1980;84(3):371–379.

144. Wierckx K, Elaut E, Van Hoerde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med*. 2014;11(1):107–118.

145. Chiriacò G, Cauci S, Mazzon G, Trombetta C. An observational retrospective evaluation of 79 young men with long-term adverse effects after use of finasteride against androgenetic alopecia. *Andrology*. 2016;4(2):245–250.

146. Gava G, Cerpolini S, Martelli V, Battista G, Seracchioli R, Meriggiola MC. Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. *Clin Endocrinol (Oxf)*. 2016; 85(2):239–246.

147. Casper RF, Yen SS. Rapid absorption of micronized estradiol-17 beta following sublingual administration. *Obstet Gynecol*. 1981; 57(1):62–64.

148. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R, Bates GW. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 β -estradiol. *Obstet Gynecol*. 1997;89(3): 340–345.

149. Toorians AWFT, Thomassen MCLGD, Zweegman S, Magdeleyns EJP, Tans G, Gooren LJG, Rosing J. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. *J Clin Endocrinol Metab*. 2003;88(12): 5723–5729.

150. Mepham N, Bouman WP, Arcelus J, Hayter M, Wylie KR. People with gender dysphoria who self-prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. *J Sex Med*. 2014; 11(12):2995–3001.

151. Richards C, Bouman WP, Seal L, Barker MJ, Nieder TO, T'Sjoen G. Non-binary or genderqueer genders. *Int Rev Psychiatry*. 2016; 28(1):95–102.

152. Cosyns M, Van Borsel J, Wierckx K, Dedecker D, Van de Peer F, Daelman T, Laenen S, T'Sjoen G. Voice in female-to-male transsexual persons after long-term androgen therapy. *Laryngoscope*. 2014;124(6):1409–1414.

153. Deuster D, Matulat P, Knief A, Zitzmann M, Rosslau K, Szukaj M, am Zehnhoff-Dinnesen A, Schmidt CM. Voice deepening under testosterone treatment in female-to-male gender dysphoric individuals. *Eur Arch Otorhinolaryngol*. 2016;273(4):959–965.

154. Lapauw B, Taes Y, Simoens S, Van Caenegem E, Weyers S, Goemaere S, Toye K, Kaufman J-M, T'Sjoen GG. Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. *Bone*. 2008;43(6):1016–1021.

155. Meyer III WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav*. 1986;15(2): 121–138.

156. Asscheman H, Gooren LJ, Assies J, Smits JP, de Slegte R. Prolactin levels and pituitary enlargement in hormone-treated male-to-female transsexuals. *Clin Endocrinol (Oxf)*. 1988;28(6):583–588.

157. Gooren LJ, Harmsen-Louman W, van Kessel H. Follow-up of prolactin levels in long-term oestrogen-treated male-to-female transsexuals with regard to prolactinoma induction. *Clin Endocrinol (Oxf)*. 1985;82(2):201–207.

158. Wierckx K, Van Caenegem E, Schreiner T, Haraldsen I, Fisher AD, Toye K, Kaufman JM, T'Sjoen G. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *J Sex Med*. 2014;11(8):1999–2011.

159. Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. *Fertil Steril*. 2010;93(4):1267–1272.

160. Giltay EJ, Hoogeveen EK, Elbers JMH, Gooren LJG, Asscheman H, Stehouwer CDA. Effects of sex steroids on plasma total homocysteine levels: a study in transsexual males and females. *J Clin Endocrinol Metab*. 1998;83(2):550–553.

161. van Kesteren PJM, Asscheman H, Megens JAJ, Gooren LJG. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997;47(3): 337–343.

162. Wierckx K, Gooren L, T'Sjoen G. Clinical review: breast development in trans women receiving cross-sex hormones. *J Sex Med*. 2014;11(5):1240–1247.

163. Bird D, Vowles K, Anthony PP. Spontaneous rupture of a liver cell adenoma after long term methyltestosterone: report of a case successfully treated by emergency right hepatic lobectomy. *Br J Surg*. 1979;66(3):212–213.

164. Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. *Lancet*. 1977; 2(8032):262–263.

165. Weinand JD, Safer JD. Hormone therapy in transgender adults is safe with provider supervision; a review of hormone therapy sequelae for transgender individuals. *J Clin Transl Endocrinol*. 2015;2(2):55–60.

166. Roberts TK, Kraft CS, French D, Ji W, Wu AH, Tangpricha V, Fantz CR. Interpreting laboratory results in transgender patients on hormone therapy. *Am J Med*. 2014;127(2):159–162.

167. Vesper HW, Botelho JC, Wang Y. Challenges and improvements in testosterone and estradiol testing. *Asian J Androl*. 2014;16(2): 178–184.

168. Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola MC, Mueller A, Kuhn A, Dhejne C, Morel-Journel N, Gooren LJ. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia*. 2014;46(7):791–795.

169. Righini M, Perrier A, De Moerloose P, Bounameaux H. D-dimer for venous thromboembolism diagnosis: 20 years later. *J Thromb Haemost*. 2008;6(7):1059–1071.

170. Gooren LJ, Assies J, Asscheman H, de Slegte R, van Kessel H. Estrogen-induced prolactinoma in a man. *J Clin Endocrinol Metab*. 1988;66(2):444–446.

171. Kovacs K, Stefanau L, Ezzat S, Smyth HS. Prolactin-producing pituitary adenoma in a male-to-female transsexual patient with protracted estrogen administration. A morphologic study. *Arch Pathol Lab Med*. 1994;118(5):562–565.

172. Serri O, Noiseux D, Robert F, Hardy J. Lactotroph hyperplasia in an estrogen treated male-to-female transsexual patient. *J Clin Endocrinol Metab*. 1996;81(9):3177–3179.

173. Cunha FS, Domenice S, Câmara VI, Sircili MH, Gooren LJ, Mendonça BB, Costa EM. Diagnosis of prolactinoma in two male-to-female transsexual subjects following high-dose cross-sex hormone therapy. *Andrologia*. 2015;47(6):680–684.

174. Nota NM, Dekker MJHJ, Klaiver M, Wiepjes CM, van Trotsenburg MA, Heijboer AC, den Heijer M. Prolactin levels during short- and long-term cross-sex hormone treatment: an observational study in transgender persons. *Andrologia*. 2017;49(6).

175. Bunc MC, Debono M, Giltay EJ, Verheijen AT, Diamant M, Gooren LJ. Autonomous prolactin secretion in two male-to-female transgender patients using conventional oestrogen dosages. *BMJ Case Rep*. 2009;2009:bcr0220091589.

176. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)*. 2010;72(1):1–10.

177. Berra M, Armillotta F, D'Emidio L, Costantino A, Martorana G, Pelusi G, Meriggiola MC. Testosterone decreases adiponectin

levels in female to male transsexuals. *Asian J Androl.* 2006;8(6):725–729.

178. Elbers JMH, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, Gooren LJJG. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. *Clin Endocrinol (Oxf).* 2003;158(5):562–571.
179. Giltay EJ, Lambert J, Gooren LJJG, Elbers JMH, Steyn M, Stehouwer CDA. Sex steroids, insulin, and arterial stiffness in women and men. *Hypertension.* 1999;34(4 Pt 1):590–597.
180. Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ. Induction of insulin resistance by androgens and estrogens. *J Clin Endocrinol Metab.* 1994;139(1):265–271.
181. Maraka S. Effect of sex steroids on lipids, venous thromboembolism, cardiovascular disease and mortality in transgender individuals: a systematic review and meta-analysis. Available at: <http://press.endocrine.org/doi/abs/10.1210/endo-meetings.2016.RE.15.FRI-136>. Accessed 3 July 2017.
182. Meriggiola MC, Armillotta F, Costantino A, Altieri P, Saad F, Kalhorn T, Perrone AM, Ghi T, Pelusi C, Pelusi G. Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. *J Sex Med.* 2008;5(10):2442–2453.
183. Giltay EJ, Toorians AW, Sarabdjitsingh AR, de Vries NA, Gooren LJ. Established risk factors for coronary heart disease are unrelated to androgen-induced baldness in female-to-male transsexuals. *J Endocrinol.* 2004;180(1):107–112.
184. Giltay EJ, Verhoef P, Gooren LJJG, Geleijnse JM, Schouten EG, Stehouwer CDA. Oral and transdermal estrogens both lower plasma total homocysteine in male-to-female transsexuals. *Atherosclerosis.* 2003;168(1):139–146.
185. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci.* 2005;60(11):1451–1457.
186. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285(19):2486–2497.
187. Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf).* 2010;72(2):214–231.
188. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman JM, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol.* 2015;172(2):163–171.
189. Turner A, Chen TC, Barber TW, Malabanan AO, Holick MF, Tangpricha V. Testosterone increases bone mineral density in female-to-male transsexuals: a case series of 15 subjects. *Clin Endocrinol (Oxf).* 2004;61(5):560–566.
190. van Kesteren P, Lips P, Gooren LJJG, Asscheman H, Megens J. Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. *Clin Endocrinol (Oxf).* 1998;48(3):347–354.
191. Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman JM, Schreiner T, Haraldsen I, T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone.* 2013;54(1):92–97.
192. Amin S, Zhang Y, Sawin CT, Evans SR, Hannan MT, Kiel DP, Wilson PW, Felson DT. Association of hypogonadism and estradiol levels with bone mineral density in elderly men from the Framingham study. *Ann Intern Med.* 2000;133(12):951–963.
193. Gennari L, Khosla S, Bilezikian JP. Estrogen and fracture risk in men. *J Bone Miner Res.* 2008;23(10):1548–1551.
194. Khosla S, Melton LJ III, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. *J Clin Endocrinol Metab.* 1998;83(7):2266–2274.
195. Mueller A, Dittrich R, Binder H, Kuehnel W, Maltaris T, Hoffmann I, Beckmann MW. High dose estrogen treatment increases bone mineral density in male-to-female transsexuals receiving gonadotropin-releasing hormone agonist in the absence of testosterone. *Eur J Endocrinol.* 2005;153(1):107–113.
196. Ruetsche AG, Kneubuehl R, Birkhaeuser MH, Lippuner K. Cortical and trabecular bone mineral density in transsexuals after long-term cross-sex hormonal treatment: a cross-sectional study. *Osteoporos Int.* 2005;16(7):791–798.
197. Ganly I, Taylor EW. Breast cancer in a trans-sexual man receiving hormone replacement therapy. *Br J Surg.* 1995;82(3):341.
198. Pritchard TJ, Pankowsky DA, Crowe JP, Abdul-Karim FW. Breast cancer in a male-to-female transsexual. A case report. *JAMA.* 1988;259(15):2278–2280.
199. Symmers WS. Carcinoma of breast in trans-sexual individuals after surgical and hormonal interference with the primary and secondary sex characteristics. *BMJ.* 1968;2(5597):83–85.
200. Brown GR. Breast cancer in transgender veterans: a ten-case series. *LGBT Health.* 2015;2(1):77–80.
201. Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. *Clin Breast Cancer.* 2011;11(6):417–419.
202. Nikolic DV, Djordjevic ML, Granic M, Nikolic AT, Stanimirovic VV, Zdravkovic D, Jelic S. Importance of revealing a rare case of breast cancer in a female to male transsexual after bilateral mastectomy. *World J Surg Oncol.* 2012;10:280.
203. Bösze P, Tóth A, Török M. Hormone replacement and the risk of breast cancer in Turner's syndrome. *N Engl J Med.* 2006;355(24):2599–2600.
204. Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA; UK Clinical Cytogenetics Group. Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study. *Lancet Oncol.* 2008;9(3):239–246.
205. Smith RA, Cokkinides V, Eye HJ. American Cancer Society guidelines for the early detection of cancer, 2006. *CA Cancer J Clin.* 2006;56(1):11–25, quiz 49–50.
206. Wilson JD, Roehrborn C. Long-term consequences of castration in men: lessons from the Skoptzy and the eunuchs of the Chinese and Ottoman courts. *J Clin Endocrinol Metab.* 1999;84(12):4324–4331.
207. van Kesteren P, Meinhardt W, van der Valk P, Geldof A, Megens J, Gooren L. Effects of estrogens only on the prostates of aging men. *J Urol.* 1996;156(4):1349–1353.
208. Brown JA, Wilson TM. Benign prostatic hyperplasia requiring transurethral resection of the prostate in a 60-year-old male-to-female transsexual. *Br J Urol.* 1997;80(6):956–957.
209. Casella R, Bubendorf L, Schaefer DJ, Bachmann A, Gasser TC, Sulser T. Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int.* 2005;75(3):288–290.
210. Dorff TB, Shazer RL, Nepomuceno EM, Tucker SJ. Successful treatment of metastatic androgen-independent prostate carcinoma in a transsexual patient. *Clin Genitourin Cancer.* 2007;5(5):344–346.
211. Thurston AV. Carcinoma of the prostate in a transsexual. *Br J Urol.* 1994;73(2):217.

212. van Harst EP, Newling DW, Gooren LJ, Asscheman H, Prenger DM. Metastatic prostatic carcinoma in a male-to-female transsexual. *BJU Int.* 1998;81:776.

213. Turo R, Jallad S, Prescott S, Cross WR. Metastatic prostate cancer in transsexual diagnosed after three decades of estrogen therapy. *Can Urol Assoc J.* 2013;7(7–8):E544–E546.

214. Miksad RA, Bubley G, Church P, Sanda M, Rofsky N, Kaplan I, Cooper A. Prostate cancer in a transgender woman 41 years after initiation of feminization. *JAMA.* 2006;296(19):2316–2317.

215. Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2012;157(2):120–134.

216. Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav.* 1998; 27(2):209–226.

217. Miller N, Bédard YC, Cooter NB, Shaul DL. Histological changes in the genital tract in transsexual women following androgen therapy. *Histopathology.* 1986;10(7):661–669.

218. O'Hanlan KA, Dibble SL, Young-Spint M. Total laparoscopic hysterectomy for female-to-male transsexuals. *Obstet Gynecol.* 2007;110(5):1096–1101.

219. Dizon DS, Tejada-Berges T, Koelliker S, Steinhoff M, Granai CO. Ovarian cancer associated with testosterone supplementation in a female-to-male transsexual patient. *Gynecol Obstet Invest.* 2006; 62(4):226–228.

220. Hage JJ, Dekker JJML, Karim RB, Verheijen RHM, Bloemena E. Ovarian cancer in female-to-male transsexuals: report of two cases. *Gynecol Oncol.* 2000;76(3):413–415.

221. Mueller A, Gooren L. Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol.* 2008;159(3):197–202.

222. Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuyperé G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfaefflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgenderism.* 2012;13:165–232.

223. Colebunders B, D'Arpa S, Weijers S, Lumen N, Hoebeke P, Monstrey S. Female-to-male gender reassignment surgery. In: Ettner R, Monstrey S, Coleman E, eds. *Principles of Transgender Medicine and Surgery.* 2nd ed. New York, NY: Routledge Taylor & Francis Group; 2016:279–317.

224. Monstrey S, Hoebeke P, Dhont M, De Cuyperé G, Rubens R, Moerman M, Hamdi M, Van Landuyt K, Blondeel P. Surgical therapy in transsexual patients: a multi-disciplinary approach. *Acta Chir Belg.* 2001;101(5):200–209.

225. Selvaggi G, Ceulemans P, De Cuyperé G, VanLanduyt K, Blondeel P, Hamdi M, Bowman C, Monstrey S. Gender identity disorder: general overview and surgical treatment for vaginoplasty in male-to-female transsexuals. *Plast Reconstr Surg.* 2005;116(6): 135e–145e.

226. Tugnet N, Goddard JC, Vickery RM, Khoosal D, Terry TR. Current management of male-to-female gender identity disorder in the UK. *Postgrad Med J.* 2007;83(984):638–642.

227. Horbach SER, Bouman M-B, Smit JM, Özer M, Buncamper ME, Mullender MG. Outcome of vaginoplasty in male-to-female transgenders: a systematic review of surgical techniques. *J Sex Med.* 2015;12(6):1499–1512.

228. Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. *Curr Opin Endocrinol Diabetes Obes.* 2013; 20(6):570–574.

229. Morrison SD, Satterwhite T, Grant DW, Kirby J, Laub DR, Sr, VanMaasdam J. Long-term outcomes of rectosigmoid neocolporrhaphy in male-to-female gender reassignment surgery. *Plast Reconstr Surg.* 2015;136(2):386–394.

230. Dessy LA, Mazzocchi M, Corrias F, Ceccarelli S, Marchese C, Scuderi N. The use of cultured autologous oral epithelial cells for vaginoplasty in male-to-female transsexuals: a feasibility, safety, and advantageousness clinical pilot study. *Plast Reconstr Surg.* 2014;133(1):158–161.

231. Li FY, Xu YS, Zhou CD, Zhou Y, Li SK, Li Q. Long-term outcomes of vaginoplasty with autologous buccal micromucosa. *Obstet Gynecol.* 2014;123(5):951–956.

232. Kanhai RC. Sensate vagina pedicled-spot for male-to-female transsexuals: the experience in the first 50 patients. *Aesthetic Plast Surg.* 2016;40(2):284–287.

233. Straayer C. Transplants for transsexuals? Ambitions, concerns, ideology. Paper presented at: Trans*Studies: An International Transdisciplinary Conference on Gender, Embodiment, and Sexuality; 7–10 September 2016; University of Arizona, Tucson, AZ.

234. Bucci S, Mazzon G, Liguori G, Napoli R, Pavan N, Bormioli S, Ollandini G, De Concilio B, Trombetta C. Neovaginal prolapse in male-to-female transsexuals: an 18-year-long experience. *Biomed Res Int.* 2014;2014:240761.

235. Raigosa M, Avvedimento S, Yoon TS, Cruz-Gimeno J, Rodriguez G, Fontdevila J. Male-to-female genital reassignment surgery: a retrospective review of surgical technique and complications in 60 patients. *J Sex Med.* 2015;12(8):1837–1845.

236. Green R. Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res.* 1998;10(Suppl 1): S22–S24.

237. Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztsbl Int.* 2014;111(47):795–801.

238. Nygren U, Nordenskjold A, Arver S, Sodersten M. Effects on voice fundamental frequency and satisfaction with voice in trans men during testosterone treatment—a longitudinal study. *J Voice.* 2016;30(6):766.e23–766.e34.

239. Becking AG, Tuininga DB, Hage JJ, Gooren LJG. Transgender feminization of the facial skeleton. *Clin Plast Surg.* 2007;34(3): 557–564.

240. Giraldo F, Esteva I, Bergero T, Cano G, González C, Salinas P, Rivada E, Lara JS, Sorriguer F; Andalusia Gender Team. Corona glans clitoroplasty and urethropreputial vestibuloplasty in male-to-female transsexuals: the vulval aesthetic refinement by the Andalusia Gender Team. *Plast Reconstr Surg.* 2004;114(6): 1543–1550.

241. Goddard JC, Vickery RM, Terry TR. Development of feminizing genitoplasty for gender dysphoria. *J Sex Med.* 2007;4(4 Pt 1): 981–989.

242. Hage JJ, de Graaf FH, Bouman FG, Bloem JJAM. Sculpturing the glans in phalloplasty. *Plast Reconstr Surg.* 1993;92(1):157–161, discussion 162.

243. Thiagaraj D, Gunasegaram R, Loganath A, Peh KL, Kottegoda SR, Ratnam SS. Histopathology of the testes from male transsexuals on oestrogen therapy. *Ann Acad Med Singapore.* 1987; 16(2):347–348.

244. Monstrey SJ, Ceulemans P, Hoebeke P. Sex reassignment surgery in the female-to-male transsexual. *Semin Plast Surg.* 2011;25(3): 229–244.

245. Perovic SV, Djinovic R, Bumbasirevic M, Djordjevic M, Vukovic P. Total phalloplasty using a musculocutaneous latissimus dorsi flap. *BJU Int.* 2007;100(4):899–905, discussion 905.

246. Vesely J, Hyza P, Ranno R, Cigna E, Monni N, Stupka I, Justan I, Dvorak Z, Novak P, Ranno S. New technique of total phalloplasty with reinnervated latissimus dorsi myocutaneous free flap in female-to-male transsexuals. *Ann Plast Surg.* 2007;58(5): 544–550.

247. Ranno R, Vesely J, Hyza P, Stupka I, Justan I, Dvorak Z, Monni N, Novak P, Ranno S. Neo-phalloplasty with re-innervated latissimus dorsi free flap: a functional study of a novel technique. *Acta Chir Plast.* 2007;49(1):3–7.

248. Garcia MM, Christopher NA, De Luca F, Spilotros M, Ralph DJ. Overall satisfaction, sexual function, and the durability of neophallus dimensions following staged female to male genital gender confirming surgery: the Institute of Urology, London U.K. experience. *Transl Androl Urol.* 2014;3(2):156–162.

249. Chen H-C, Gedebou TM, Yazar S, Tang Y-B. Prefabrication of the free fibula osteocutaneous flap to create a functional human penis using a controlled fistula method. *J Reconstr Microsurg.* 2007; 23(3):151–154.

250. Hoebeke PB, Decaestecker K, Beyens M, Opdenakker Y, Lumen N, Monstrey SM. Erectile implants in female-to-male transsexuals: our experience in 129 patients. *Eur Urol.* 2010;57(2): 334–341.

251. Hage JJ. Metaidoiplasty: an alternative phalloplasty technique in transsexuals. *Plast Reconstr Surg.* 1996;97(1):161–167.

252. Cohanzad S. Extensive metoidioplasty as a technique capable of creating a compatible analogue to a natural penis in female transsexuals. *Aesthetic Plast Surg.* 2016;40(1):130–138.

253. Selvaggi G, Hoebeke P, Ceulemans P, Hamdi M, Van Landuyt K, Blondeel P, De Cuyper G, Monstrey S. Scrotal reconstruction in female-to-male transsexuals: a novel scrotoplasty. *Plast Reconstr Surg.* 2009;123(6):1710–1718.

254. Bjerrome Ahlin H, Kölby L, Elander A, Selvaggi G. Improved results after implementation of the Ghent algorithm for subcutaneous mastectomy in female-to-male transsexuals. *J Plast Surg Hand Surg.* 2014;48(6):362–367.

255. Wolter A, Diedrichson J, Scholz T, Arens-Landwehr A, Liebau J. Sexual reassignment surgery in female-to-male transsexuals: an algorithm for subcutaneous mastectomy. *J Plast Reconstr Aesthet Surg.* 2015;68(2):184–191.

256. Richards C, Barrett J. The case for bilateral mastectomy and male chest contouring for the female-to-male transsexual. *Ann R Coll Surg Engl.* 2013;95(2):93–95.

257. Sutcliffe PA, Dixon S, Akehurst RL, Wilkinson A, Shippam A, White S, Richards R, Caddy CM. Evaluation of surgical procedures for sex reassignment: a systematic review. *J Plast Reconstr Aesthet Surg.* 2009;62(3):294–306, discussion 306–308.

258. Selvaggi G, Elander A. Penile reconstruction/formation. *Curr Opin Urol.* 2008;18(6):589–597.

259. Dhejne C, Lichtenstein P, Boman M, Johansson ALV, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One.* 2011;6(2):e16885.

260. Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller MD, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril.* 2009;92(5):1685–1689.e3.

261. Papadopoulos NA, Lellé JD, Zavlin D, Herschbach P, Henrich G, Kovacs L, Ehrenberger B, Kluger AK, Machens HG, Schaff J. Quality of life and patient satisfaction following male-to-female sex reassignment surgery. *J Sex Med.* 2017;14(5):721–730.

262. Simonsen RK, Hald GM, Kristensen E, Giraldi A. Long-term follow-up of individuals undergoing sex-reassignment surgery: somatic morbidity and cause of death. *Sex Med.* 2016;4(1): e60–e68.

263. Djordjevic ML, Bizic MR, Duisin D, Bouman MB, Buncamper M. Reversal Surgery in regretful male-to-female transsexuals after sex reassignment surgery. *J Sex Med.* 2016;13(6):1000–1007.

264. Liberopoulos EN, Florentin M, Mikhailidis DP, Elisaf MS. Compliance with lipid-lowering therapy and its impact on cardiovascular morbidity and mortality. *Expert Opin Drug Saf.* 2008;7(6):717–725.

265. Forbes SS, Stephen WJ, Harper WL, Loeb M, Smith R, Christoffersen EP, McLean RF. Implementation of evidence-based practices for surgical site infection prophylaxis: results of a pre- and postintervention study. *J Am Coll Surg.* 2008;207(3): 336–341.

266. Davis PJ, Spady D, de Gara C, Forgie SE. Practices and attitudes of surgeons toward the prevention of surgical site infections: a provincial survey in Alberta, Canada. *Infect Control Hosp Epidemiol.* 2008;29(12):1164–1166.